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By Allen Frances, Harold Alan Pincus, Thomas A. Widiger, et al.

A Critical Review of Epidemiological Studies
of Puerto Rican Mental Health

By Peter J. Guarnaccia, Byron J. Good, and Arthur Kleinman

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New Policy of Structured Abstracts

Effective with the January 1991 issue, *The American Journal of Psychiatry* will institute a policy of structured abstracts for Special Articles and Regular Articles. Authors of review articles must include the following information, under the headings indicated: *Objective*—the primary purpose of the review article; *Method*—data sources, study selection (the number of studies selected for review and how they were selected), data extraction (rules for abstracting data and how they were applied); *Results*—methods of data synthesis, key findings; and *Conclusions*—including potential applications and research needs. Authors of research articles must include *Objective*—questions addressed by the study; *Method*—design of the study, setting (location and level of clinical care), patients or participants (manner of selection and number who entered and completed the study), interventions (if any), main outcome measures (primary study outcome measure as planned before data collection); *Results*—key findings; and *Conclusions*—including direct clinical applications. Other types of articles, including Clinical and Research Reports, should include unstructured abstracts. Also effective with the January 1991 issue, the maximum number of words for abstracts for Special Articles and Regular Articles will be increased to 250 and for Clinical and Research Reports to 60.

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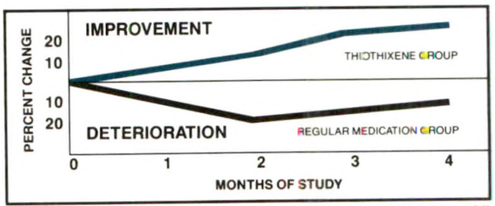

(Adapted from DiMascio and Demirgian[2,3])

Forty-two psychotic male and female patients under age 55 were entered in this study on a nonblind basis, and randomly assigned to their regular medication or switched to thiothixene. Patients were evaluated at baseline and on a daily basis, and periodically rated on the Global Improvement and Brief Psychiatric Rating Scales.

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INDICATIONS: Management of anxiety disorders, or short-term relief of symptoms of anxiety. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic. Symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology; spasticity caused by upper motor neuron disorders; athetosis; stiff-man syndrome; convulsive disorders (not as sole therapy).

The effectiveness of Valium in long-term use, that is, more than 4 months, has not been assessed by systematic clinical studies. The physician should periodically reassess the usefulness of the drug for the individual patient.

CONTRAINDICATED: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

WARNINGS: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants.

***Usage in Pregnancy:* Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Withdrawal symptoms of the barbiturate type have occurred after discontinuation of benzodiazepines (see Drug Abuse and Dependence).

PRECAUTIONS: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

The clearance of Valium and certain other benzodiazepines can be delayed in association with Tagamet (cimetidine) administration. The clinical significance of this is unclear. Inform patients to consult physician before increasing dose or abruptly discontinuing diazepam.

SIDE EFFECTS: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

Drug Abuse and Dependence: Withdrawal symptoms similar to those noted with barbiturates and alcohol have occurred following abrupt discontinuation of diazepam; more severe seen after excessive doses over extended periods; milder after taking continuously at therapeutic levels for several months. After extended therapy, avoid abrupt discontinuation and taper dosage. Carefully supervise addiction-prone individuals because of predisposition to habituation and dependence.

DOSAGE: Individualize for maximum beneficial effect. *Adults:* Anxiety disorders, symptoms of anxiety, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. *Geriatric or debilitated patients:* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) *Children:* 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).

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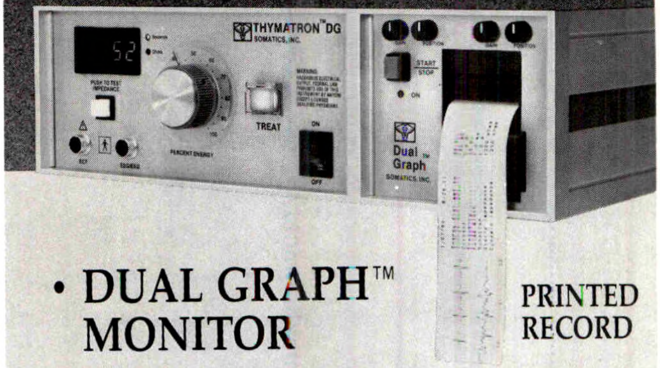

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The Déjà Vu Experience: Remembrance of Things Past?
By Herman N. Sno and Don H. Linszen

PAMELOR® (nortriptyline HCl)
BRIEF SUMMARY.
Please see package insert for full prescribing information.

Contraindications: 1) Concurrent use with a monoamine oxidase (MAO) inhibitor, since hyperpyretic crises, severe convulsions, and fatalities have occurred when similar tricyclic antidepressants were used in such combinations; MAO inhibitors should be discontinued for at least two weeks before treatment with Pamelor® (nortriptyline HCl) is started. 2) Hypersensitivity to Pamelor® (nortriptyline HCl), cross-sensitivity with other dibenzazepines is a possibility. 3) The acute recovery period after myocardial infarction.

Warnings: Give only under close supervision to patients with cardiovascular disease, because of the tendency of the drug to produce sinus tachycardia and to prolong conduction time; myocardial infarction, arrhythmia, and strokes have occurred. The antihypertensive action of guanethidine and similar agents may be blocked. Because of its anticholinergic activity, nortriptyline should be used with great caution in patients who have glaucoma or a history of urinary retention. Patients with a history of seizures should be followed closely, since nortriptyline is known to lower the convulsive threshold. Great care is required in hyperthyroid patients or those receiving thyroid medication, since cardiac arrhythmias may develop. Nortriptyline may impair the mental and/or physical abilities required for the performance of hazardous tasks, such as operating machinery or driving a car; therefore, the patient should be warned accordingly. Excessive consumption of alcohol may have a potentiating effect, which may lead to the danger of increased suicidal attempts or overdosage, especially in patients with histories of emotional disturbances or suicidal ideation.

The concomitant administration of quinidine and nortriptyline may result in a significantly longer plasma half-life, higher A.U.C. and lower clearance of nortriptyline.

Use in Pregnancy—Safe use during pregnancy and lactation has not been established; therefore, in pregnant patients, nursing mothers, or women of childbearing potential, the potential benefits must be weighed against the possible hazards.

Use in Children—Not recommended for use in children, since safety and effectiveness in the pediatric age group have not been established.

Precautions: Use in schizophrenic patients may result in an exacerbation of the psychosis or may activate latent schizophrenic symptoms; in overactive or agitated patients, increased anxiety and agitation may occur; in manic-depressive patients, symptoms of the manic phase may emerge. Administration of reserpine during therapy with a tricyclic antidepressant has been shown to produce a "stimulating" effect in some depressed patients. Troublesome patient hostility may be aroused. Epileptiform seizures may accompany administration. Close supervision and careful adjustment of dosage are required when used with other anticholinergic drugs and sympathomimetic drugs. Concurrent administration of cimetidine can produce clinically significant increases in the plasma concentrations of the tricyclic antidepressant. Patients should be informed that the response to alcohol may be exaggerated. When essential, may be administered with electroconvulsive therapy, although the hazards may be increased. Discontinue the drug for several days, if possible, prior to elective surgery. The possibility of a suicidal attempt by a depressed patient remains after the initiation of treatment; in this regard, it is important that the least possible quantity of drug be dispensed at any given time. Both elevation and lowering of blood sugar levels have been reported. A case of significant hypoglycemia has been reported in a type II diabetic patient maintained on chlorpropamide (250 mg/day), after the addition of nortriptyline (125 mg/day).

Adverse Reactions: *Cardiovascular*—Hypotension, hypertension, tachycardia, palpitation, myocardial infarction, arrhythmias, heart block, stroke. *Psychiatric*—Confusional states (especially in the elderly) with hallucinations, disorientation, delusions; anxiety, restlessness, agitation; insomnia, panic, nightmares; hypomania; exacerbation of psychosis. *Neurologic*—Numbness, tingling, paresthesias of extremities; incoordination, ataxia, tremors; peripheral neuropathy; extrapyramidal symptoms; seizures, alteration in EEG patterns; tinnitus. *Anticholinergic*—Dry mouth and, rarely, associated sublingual adenitis; blurred vision, disturbance of accommodation, mydriasis; constipation, paralytic ileus; urinary retention, delayed micturition, dilation of the urinary tract. *Allergic*—Skin rash, petechiae, urticaria, itching, photosensitization (avoid excessive exposure to sunlight); edema (general or of face and tongue), drug fever, cross-sensitivity with other tricyclic drugs. *Hematologic*—Bone marrow depression, including agranulocytosis; eosinophilia; purpura; thrombocytopenia. *Gastrointestinal*—Nausea and vomiting, anorexia, epigastric distress, diarrhea, peculiar taste, stomatitis, abdominal cramps, black-tongue. *Endocrine*—Gynecomastia in the male, breast enlargement and galactorrhea in the female; increased or decreased libido, impotence; testicular swelling; elevation or depression of blood sugar levels; syndrome of inappropriate ADH (antidiuretic hormone) secretion. *Other*—Jaundice (simulating obstructive), altered liver function; weight gain or loss; perspiration; flushing; urinary frequency, nocturia; drowsiness, dizziness, weakness, fatigue, headache; parotid swelling; alopecia. *Withdrawal Symptoms*—Though these are not indicative of addiction, abrupt cessation of treatment after prolonged therapy may produce nausea, headache, and malaise.

Overdosage: Toxic overdosage may result in confusion, restlessness, agitation, vomiting, hyperpyrexia, muscle rigidity, hyperactive reflexes, tachycardia, ECG evidence of impaired conduction, shock, congestive heart failure, stupor, coma, and CNS stimulation with convulsions followed by respiratory depression. Deaths have occurred with drugs of this class. No specific antidote is known; general supportive measures are indicated, with gastric lavage. [PAM-Z19—9/1/89]

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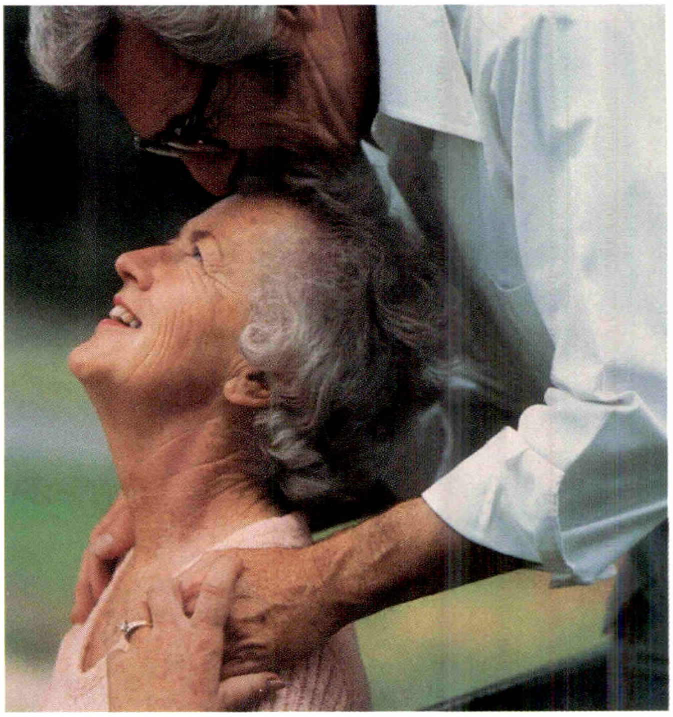

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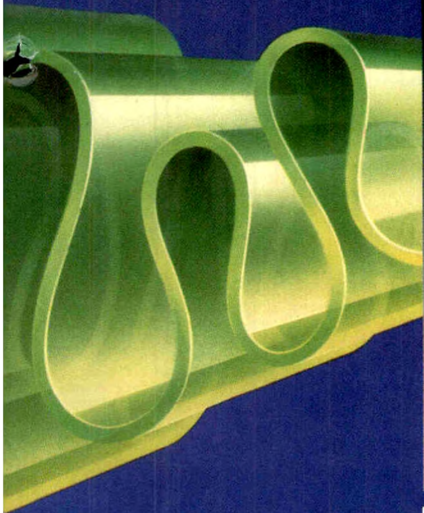

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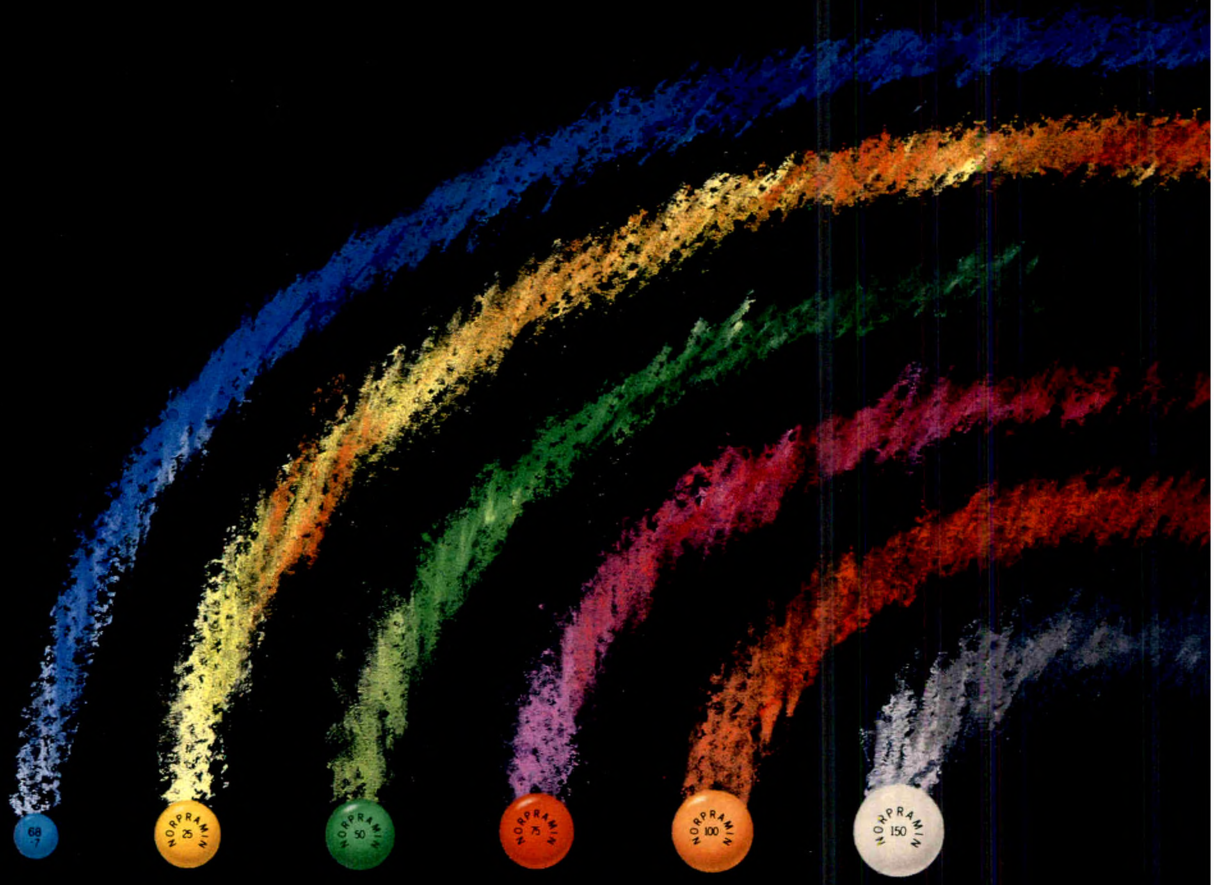

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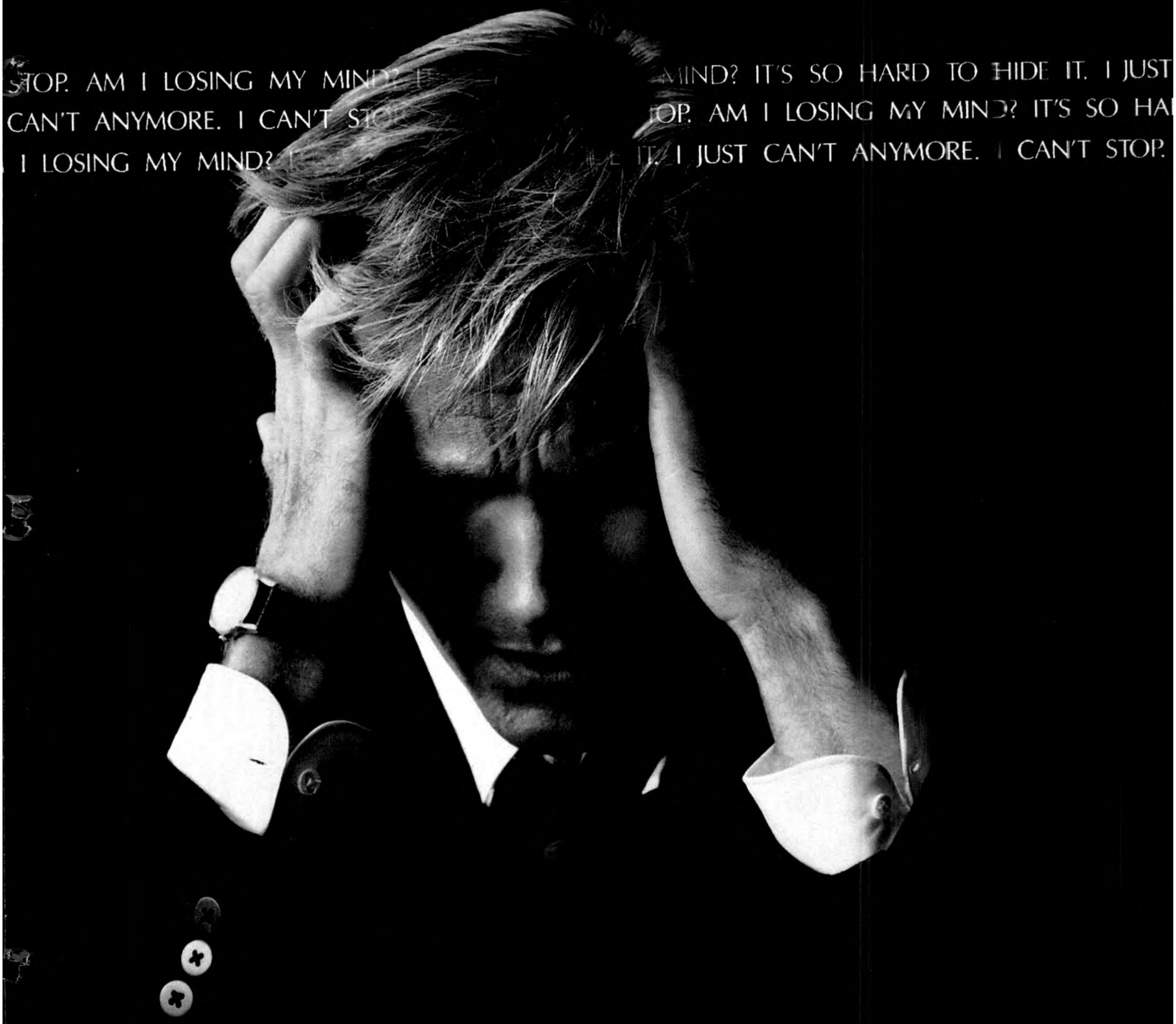
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Libido change	21	3	—	—
Nervousness	18	2	4	2
Myoclonus	13	—	2	—
Increased appetite	11	2	—	2
Paresthesia	9	3	2	2
Memory impairment	9	1	7	2
Anxiety	9	4	2	—
Twitching	7	1	4	5
Impaired concentration	5	2	—	—
Depression	5	1	—	—
Hypertonia	4	1	2	—
Sleep disorder	4	—	9	5
Psychosomatic disorder	3	—	—	—
Yawning	3	—	—	—
Confusion	3	—	2	—
Speech disorder	3	—	—	—
Abnormal dreaming	3	—	—	2
Agitation	3	—	—	—
Migraine	3	—	—	—
Depersonalization	2	—	2	—
Irritability	2	2	2	—
Emotional lability	2	—	—	2
Panic reaction	1	—	2	—
Aggressive reaction	—	—	2	—
Paresis	—	—	2	—
Skin and Appendages				
Increased sweating	29	3	9	—
Rash	8	1	4	2
Pruritus	6	—	2	2
Dermatitis	2	—	—	2
Acne	2	2	—	5
Dry skin	2	—	—	5
Urticaria	1	—	—	—
Abnormal skin odor	—	—	2	—
Digestive System				
Dry mouth	84	17	63	16
Constipation	47	11	22	9
Nausea	33	14	9	11
Dyspepsia	22	10	13	2
Diarrhea	13	9	7	5
Anorexia	12	—	22	2
Abdominal pain	11	9	13	16
Vomiting	7	2	7	—
Flatulence	6	3	—	2
Tooth disorder	5	—	—	—
Gastrointestinal disorder	2	—	—	2
Dysphagia	2	—	—	—
Esophagitis	1	—	—	—
Eructation	—	—	2	2
Ulcerative stomatitis	—	—	2	—
Body as a Whole				
Fatigue	39	18	35	9
Weight increase	18	1	2	—
Flushing	8	—	7	—
Hot flushes	5	—	2	—
Chest pain	4	4	7	—
Fever	4	—	2	7
Allergy	3	3	7	5
Pain	3	2	4	2
Local edema	2	4	—	—
Chills	2	1	—	—
Weight decrease	—	—	7	—
Otitis media	—	—	4	5
Asthenia	—	—	2	—
Halitosis	—	—	2	—
Cardiovascular System				
Postural hypotension	6	—	4	—
Palpitation	4	2	4	—
Tachycardia	4	—	2	—
Syncope	—	—	2	—
Respiratory System				
Pharyngitis	14	9	—	5
Rhinitis	12	10	7	9
Sinusitis	6	4	2	5
Coughing	6	6	4	5
Bronchospasm	2	—	7	2
Epistaxis	2	—	—	2
Dyspnea	—	—	2	—
Laryngitis	—	1	2	—
Urogenital System				
Male and Female Patients Combined				
Micturition disorder	14	2	4	2
Urinary tract infection	6	1	—	—
Micturition frequency	5	3	—	—
Urinary retention	2	—	7	—
Dysuria	2	2	—	—
Cystitis	2	—	—	—
Female Patients Only	(N = 182)	(N = 167)	(N = 10)	(N = 21)
Dysmenorrhea	12	14	10	10
Lactation (nonpuerperal)	4	—	—	—
Menstrual disorder	4	2	—	—
Vaginitis	2	—	—	—
Leukorrhea	2	—	—	—
Breast enlargement	2	—	—	—
Breast pain	1	—	—	—
Amenorrhea	1	—	—	—
Male Patients Only	(N = 140)	(N = 152)	(N = 36)	(N = 23)
Ejaculation failure	42	2	6	—
Impotence	20	3	—	—
Special Senses				
Abnormal vision	18	4	7	2
Taste perversion	8	—	4	—
Tinnitus	6	—	4	—
Abnormal lacrimation	3	2	—	—
Mydriasis	2	—	—	—
Conjunctivitis	1	—	—	—
Anisocoria	—	—	2	—
Blepharospasm	—	—	2	—
Ocular allergy	—	—	2	—
Vestibular disorder	—	—	2	2
Musculoskeletal				
Myalgia	13	9	—	—
Back pain	6	6	—	—
Arthralgia	3	5	—	—
Muscle weakness	1	—	2	—
Hemic and Lymphatic				
Purpura	3	—	—	—
Anemia	—	—	2	2
Metabolic and Nutritional				
Thirst	2	2	—	2

Other Events Observed During the Premarketing Evaluation of Anafranil

During clinical testing in the U.S., multiple doses of Anafranil were administered to approximately 3600 subjects. Untoward events associated with this exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories.

In the tabulations that follow, a modified World Health Organization dictionary of terminology has been used to classify reported adverse events. The frequencies presented, therefore, represent the proportion of the 3525 individuals exposed to Anafranil who experienced an event of the type cited on at least one occasion while receiving Anafranil. All events are included except those already listed in the previous table, those reported in terms so general as to be uninformative, and those in which an association with the drug was remote. It is important to emphasize that although the events reported occurred during treatment with Anafranil, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in less than 1/1000 patients.

Body as a Whole: *Infrequent* — general edema, increased susceptibility to infection, malaise. *Rare* — dependent edema, withdrawal syndrome.

Cardiovascular System: *Infrequent* — abnormal ECG, arrhythmia, bradycardia, cardiac arrest, extrasystoles, pallor. *Rare* — aneurysm, atrial flutter, bundle branch block, cardiac failure, cerebral hemorrhage, heart block, myocardial infarction, myocardial ischemia, peripheral ischemia, thrombophlebitis, vasospasm, ventricular tachycardia.

Digestive System: *Infrequent* — abnormal hepatic function, blood in stool, colitis, duodenitis, gastric ulcer, gastritis, gastroesophageal reflux, gingivitis, glossitis, hemorrhoids, hepatitis, increased saliva, irritable bowel syndrome, peptic ulcer, rectal hemorrhage, tongue ulceration, tooth caries. *Rare* — cheilitis, chronic enteritis, discolored feces, gastric dilatation, gingival bleeding, hiccup, intestinal obstruction, oral/pharyngeal edema, paralytic ileus, salivary gland enlargement.

Endocrine System: *Infrequent* — hypothyroidism. *Rare* — goiter, gynecomastia, hyperthyroidism.

Hemic and Lymphatic System: *Infrequent* — lymphadenopathy. *Rare* — leukemoid reaction, lymphoma-like disorder, marrow depression.

Metabolic and Nutritional Disorder: *Infrequent* — dehydration, diabetes mellitus, gout, hypercholesterolemia, hyperglycemia, hyperuricemia, hypokalemia. *Rare* — fat intolerance, glycosuria.

Musculoskeletal System: *Infrequent* — arthrosis. *Rare* — dystonia, exostosis, lupus erythematosus rash, bruising, myopathy, myositis, polyarteritis nodosa, torticollis.

Nervous System: *Frequent* — abnormal thinking, vertigo. *Infrequent* — abnormal coordination, abnormal EEG, abnormal gait, apathy, ataxia, coma, convulsions, delirium, delusion, dyskinesia, dysphonia, encephalopathy, euphoria, extrapyramidal disorder, hallucinations, hostility, hyperkinesia, hypnagogic hallucinations, hypokinesia, leg cramps, manic reaction, neuralgia, paranoia, phobic disorder, psychosis, sensory disturbance, somnambulism, stimulation, suicidal ideation, suicide attempt, teeth-grinding. *Rare* — anticholinergic syndrome, aphasia, apraxia, catalepsy, cholinergic syndrome, choreoathetosis, generalized spasm, hemiparesis, hyperesthesia, hyperreflexia, hypoesthesia, illusion, impaired impulse control, indecisiveness, mutism, neuropathy, nystagmus, oculogyric crisis, oculomotor nerve paralysis, schizophrenic reaction, stupor, suicide.

Respiratory System: *Infrequent* — bronchitis, hyperventilation, increased sputum, pneumonia. *Rare* — cyanosis, hemoptysis, hypoventilation, laryngismus.

Skin and Appendages: *Infrequent* — alopecia, cellulitis, cyst, eczema, erythematous rash, genital pruritus, maculopapular rash, photosensitivity reaction, psoriasis, pustular rash, skin discoloration. *Rare* — chloasma, folliculitis, hypertrichosis, piloerection, seborrhea, skin hypertrophy, skin ulceration.

Special Senses: *Infrequent* — abnormal accommodation, deafness, diplopia, earache, eye pain, foreign body sensation, hyperacusis, parosmia, photophobia, scleritis, taste loss. *Rare* — blepharitis, chromatopsia, conjunctival hemorrhage, exophthalmos, glaucoma, keratitis, labyrinth disorder, night blindness, retinal disorder, strabismus, visual field defect.

Urogenital System: *Infrequent* — endometriosis, epididymitis, hematuria, nocturia, oliguria, ovarian cyst, perineal pain, polyuria, prostatic disorder, renal calculus, renal pain, testis disorder, urethral disorder, urinary incontinence, uterine hemorrhage, vaginal hemorrhage. *Rare* — albuminuria, anorgasmy, breast engorgement, breast fibroadenosis, cervical dysplasia, endometrial hyperplasia, premature ejaculation, pyelonephritis, pyuria, renal cyst, uterine inflammation, vulvar disorder.

DRUG ABUSE AND DEPENDENCE

Anafranil has not been systematically studied in animals or humans for its potential for abuse, tolerance, or physical dependence. While a variety of withdrawal symptoms have been described in association with Anafranil discontinuation (see PRECAUTIONS, Withdrawal Symptoms), there is no evidence for drug-seeking behavior, except for a single report of potential Anafranil abuse by a patient with a history of dependence on codeine, benzodiazepines, and multiple psychoactive drugs. The patient received Anafranil for depression and panic attacks and appeared to become dependent after hospital discharge.

Despite the lack of evidence suggesting an abuse liability for Anafranil in foreign marketing, it is not possible to predict the extent to which Anafranil might be misused or abused once marketed in the U.S. Consequently, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely.

OVERDOSAGE

Human Experience

In U.S. clinical trials, 2 deaths occurred in 12 reported cases of acute overdosage with Anafranil either alone or in combination with other drugs. One death involved a patient suspected of ingesting a dose of 7000 mg. The second death involved a patient suspected of ingesting a dose of 5750 mg. The 10 nonfatal cases involved doses of up to 5000 mg, accompanied by plasma levels of up to 1010 ng/ml. All 10 patients completely recovered. Among reports from other countries of Anafranil overdose, the lowest dose associated with a fatality was 750 mg. Based upon post-marketing reports in the United Kingdom, CMI's lethality in overdose is considered to be similar to that reported for closely related tricyclic compounds marketed as antidepressants.

Signs and Symptoms

Signs and symptoms vary in severity depending upon factors such as the amount of drug absorbed, the age of the patient, and the time elapsed since drug ingestion. Blood and urine levels of Anafranil may not reflect the severity of poisoning: they have chiefly a qualitative rather than quantitative value, and they are unreliable indicators in the clinical management of the patient. The first signs and symptoms of poisoning with tricyclic antidepressants are generally severe anticholinergic reactions. CNS abnormalities may include drowsiness, stupor, coma, ataxia, restlessness, agitation, delirium, severe perspiration, hyperactive reflexes, muscle rigidity, athetoid and choreiform movements, and convulsions. Cardiac abnormalities may include arrhythmia, tachycardia, ECG evidence of impaired conduction, and signs of congestive heart failure, and in very rare cases, cardiac arrest. Respiratory depression, cyanosis, hypotension,shock, vomiting, hyperpyrexia, mydriasis, oliguria or anuria, and diaphoresis may also be present.

Treatment

The recommended treatment for tricyclic overdose may change periodically. Therefore, it is recommended that the physician contact a poison control center for current information on treatment.

Because CNS involvement, respiratory depression, and cardiac arrhythmia can occur suddenly, hospitalization and close observation are necessary, even when the amount ingested is thought to be small or the initial degree of intoxication appears slight or moderate. All patients with ECG abnormalities should have continuous cardiac monitoring for at least 72 hours and be closely observed until well after the cardiac status has returned to normal; relapses may occur after apparent recovery. The slow intravenous administration of physostigmine salicylate has been reported to reverse the cardiovascular and CNS anticholinergic manifestations of tricyclic overdosage; however, it should not be used routinely, since it may induce seizures and cholinergic crises and there is persisting debate about its net utility.

In the alert patient, the stomach should be emptied promptly by induced emesis followed by lavage. In the obtunded patient, the airway should be secured with a cuffed endotracheal tube before beginning lavage (do not induce emesis). Lavage should be continued for 24 hours or longer, depending on the apparent severity of intoxication. Normal or half-normal saline should be used to avoid water intoxication, especially in children. Instillation of activated charcoal slurry may help reduce absorption of CMI.

External stimulation should be minimized to reduce the tendency for convulsions, and anticonvulsants may be necessary. If MAO inhibitors have been taken recently, barbiturates should not be used. Adequate respiratory exchange should be maintained, including intubation and artificial respiration, if necessary. Respiratory stimulants should not be used.

In severe hypotension or shock, the patient should be placed in an appropriate position and given a plasma expander, dopamine, or dobutamine by intravenous drip. The use of corticosteroids in shock is controversial and may be contraindicated in cases of overdosage with tricyclic antidepressants. Digitalis may increase conduction abnormalities and further irritate an already sensitized myocardium. If congestive heart failure necessitates rapid digitalization, particular care must be exercised. Hyperpyrexia should be controlled by whatever external means are available, including ice packs and cooling sponge baths, if necessary. Hemodialysis, peritoneal dialysis, exchange transfusions, and forced diuresis have generally been reported as ineffective because of the rapid fixation of Anafranil in tissues.

DOSAGE AND ADMINISTRATION

The treatment regimens described below are based on those used in controlled clinical trials of Anafranil in 520 adults, and 91 children and adolescents with OCD. During initial titration, Anafranil should be given in divided doses with meals to reduce gastrointestinal side effects. The goal of this initial titration phase is to minimize side effects by permitting tolerance to side effects to develop or allowing the patient time to adapt if tolerance does not develop.

Because both CMI and its active metabolite, DMI, have long elimination half-lives, the prescriber should take into consideration the fact that steady-state plasma levels may not be achieved until 2-3 weeks after dosage change (see CLINICAL PHARMACOLOGY). Therefore, after initial titration, it may be appropriate to wait 2-3 weeks between further dosage adjustments.

Initial Treatment/Dose Adjustment (Adults)

Treatment with Anafranil should be initiated at a dosage of 25 mg daily and gradually increased, as tolerated, to approximately 100 mg during the first 2 weeks. During initial titration, Anafranil should be given in divided doses with meals to reduce gastrointestinal side effects. Thereafter, the dosage may be increased gradually over the next several weeks, up to a maximum of 250 mg daily. After titration, the total daily dose may be given once daily at bedtime to minimize daytime sedation.

Initial Treatment/Dose Adjustment (Children and Adolescents)

As with adults, the starting dose is 25 mg daily and should be gradually increased (also given in divided doses with meals to reduce gastrointestinal side effects) during the first 2 weeks, as tolerated, up to a daily maximum of 3 mg/kg or 100 mg, whichever is smaller. Thereafter, the dosage may be increased gradually over the next several weeks up to a daily maximum of 3 mg/kg or 200 mg, whichever is smaller (see PRECAUTIONS, Pediatric Use). As with adults, after titration, the total daily dose may be given once daily at bedtime to minimize daytime sedation.

Maintenance/Continuation Treatment (Adults, Children, and Adolescents)

While there are no systematic studies that answer the question of how long to continue Anafranil, OCD is a chronic condition and it is reasonable to consider continuation for a responding patient. Although the efficacy of Anafranil after 10 weeks has not been documented in controlled trials, patients have been continued in therapy under double-blind conditions for up to 1 year without loss of benefit. However, dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for treatment. During maintenance, the total daily dose may be given once daily at bedtime.

HOW SUPPLIED

Capsules 25 mg — ivory/melon yellow (imprinted ANAFRANIL 25 mg)
Bottles of 100 .... NDC 0083-0115-30
Unit Dose (blister pack)
Box of 100 (strips of 10) .... NDC 0083-0115-32
Capsules 50 mg — ivory/aqua blue (imprinted ANAFRANIL 50 mg)
Bottles of 100 .... NDC 0083-0116-30
Unit Dose (blister pack)
Box of 100 (strips of 10) .... NDC 0083-0116-32
Capsules 75 mg — ivory/yellow (imprinted ANAFRANIL 75 mg)
Bottles of 100 .... NDC 0083-0117-30
Unit Dose (blister pack)
Box of 100 (strips of 10) .... NDC 0083-0117-32

Do not store above 86°F (30°C). Protect from moisture.

Dispense in tight container (USP).

ANIMAL TOXICOLOGY

Testicular and lung changes commonly associated with tricyclic compounds have been observed with Anafranil. In 1- and 2-year studies in rats, changes in the testes (atrophy, aspermatogenesis, and calcification) and drug-induced phospholipidosis in the lungs were observed at doses 4 times the maximum daily human dose. Testicular atrophy was also observed in a 1-year oral toxicity study in dogs at 10 times the maximum daily human dose.

C90-1

C I B A

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Division of CIBA-GEIGY Corporation
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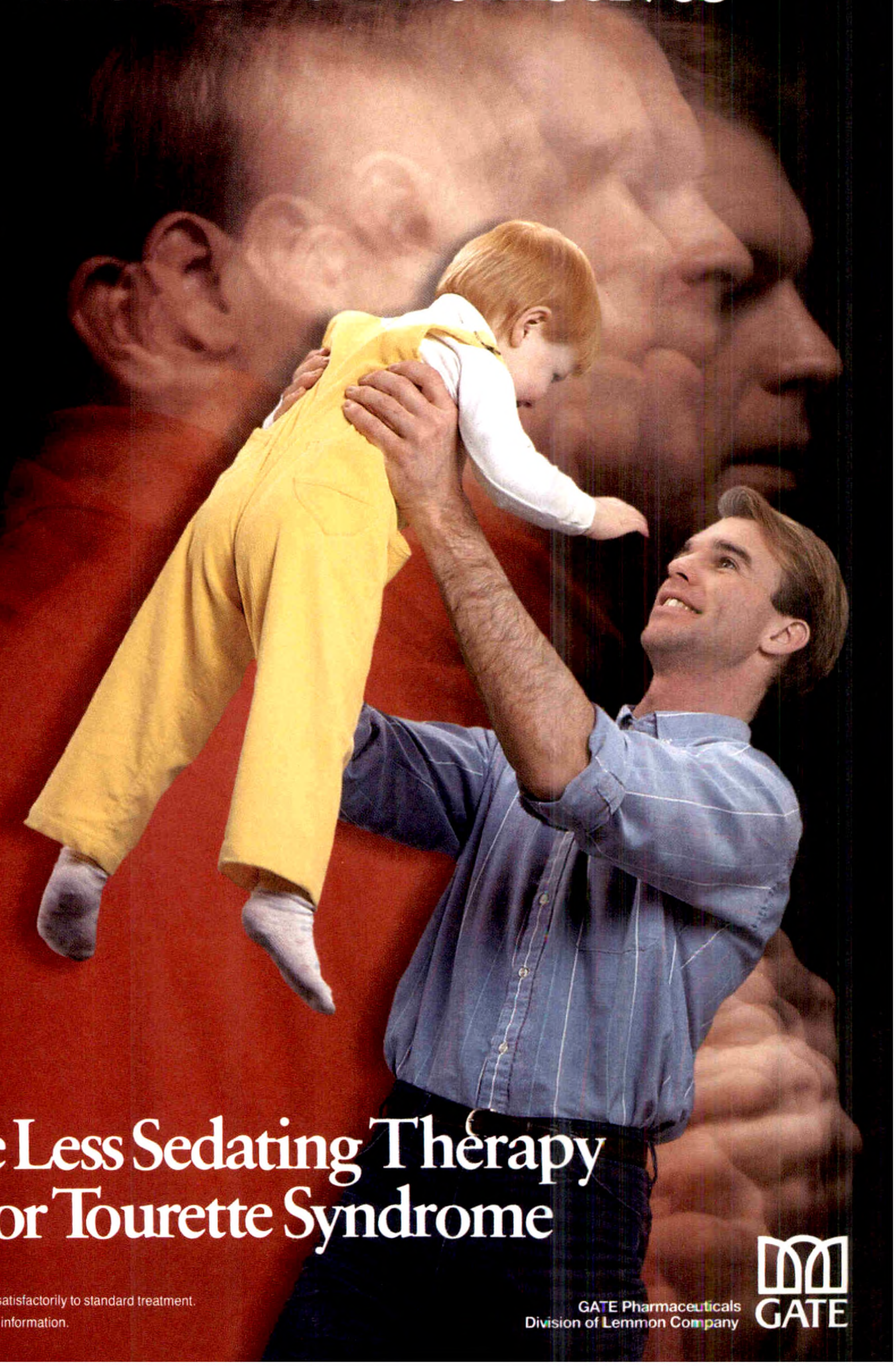
* Events reported by at least 1% of Anafranil patients are included

In Tourette Syndrome ORAP™ (pimozide) Tablets Helps Patients Be Themselves*



- Excellent Symptom Control

"Pimozide produced significantly more improvement of symptoms and less akinesic adverse effects than haloperidol. . . . Improvement of 70% or more was reported by 74% of patients on pimozide compared with 45% on haloperidol ($p < .02$), and 84% rated pimozide better overall than haloperidol."[1]

- Significantly Less Sedation than Haloperidol

In a double-blind, placebo-controlled study, "Pimozide was associated with lethargy or tiredness on significantly fewer days than haloperidol ($p < .01$), and this was reflected in greater immediate and long-term patient acceptance . . ."[2]

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* ORAP is indicated for patients who have failed to respond satisfactorily to standard treatment.
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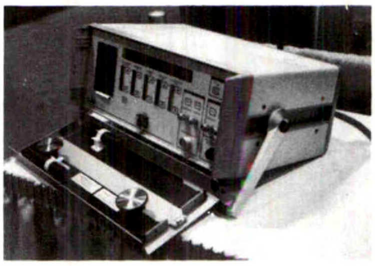

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Call for Nominations

The Institute of Living is pleased to announce that nominations are now being accepted for the 1991 C. Charles Burlingame Award. This award, given to honor an outstanding leader in psychiatric education and research, is made in the memory of Dr. Burlingame, psychiatrist-in-chief from 1931 to 1950.

We invite you to nominate a person who has significantly advanced the field of psychiatry through creative teaching or research. The nomination must include a current curriculum vitae and two letters of support describing the candidate's achievements.

The winner of the Burlingame Award will be notified by January 30, 1991 and invited to present an original research paper as the focal point of the award day events. The award, which will be presented at The Institute in April 1991, includes a commemorative certificate and a $2000 honorarium, plus expenses.

The Institute of Living is a fully accredited teaching hospital with inpatient, outpatient and residential programs for patients of all ages. In its 168-year history, The Institute has established a reputation as one of the country's foremost psychiatric centers for patient care, education, and research.

Nominations should be
sent no later than
January 15, 1991 to:

William L. Webb, Jr., M.D.
Psychiatrist-in-Chief
The Institute of Living
400 Washington Street
Hartford, CT 06106

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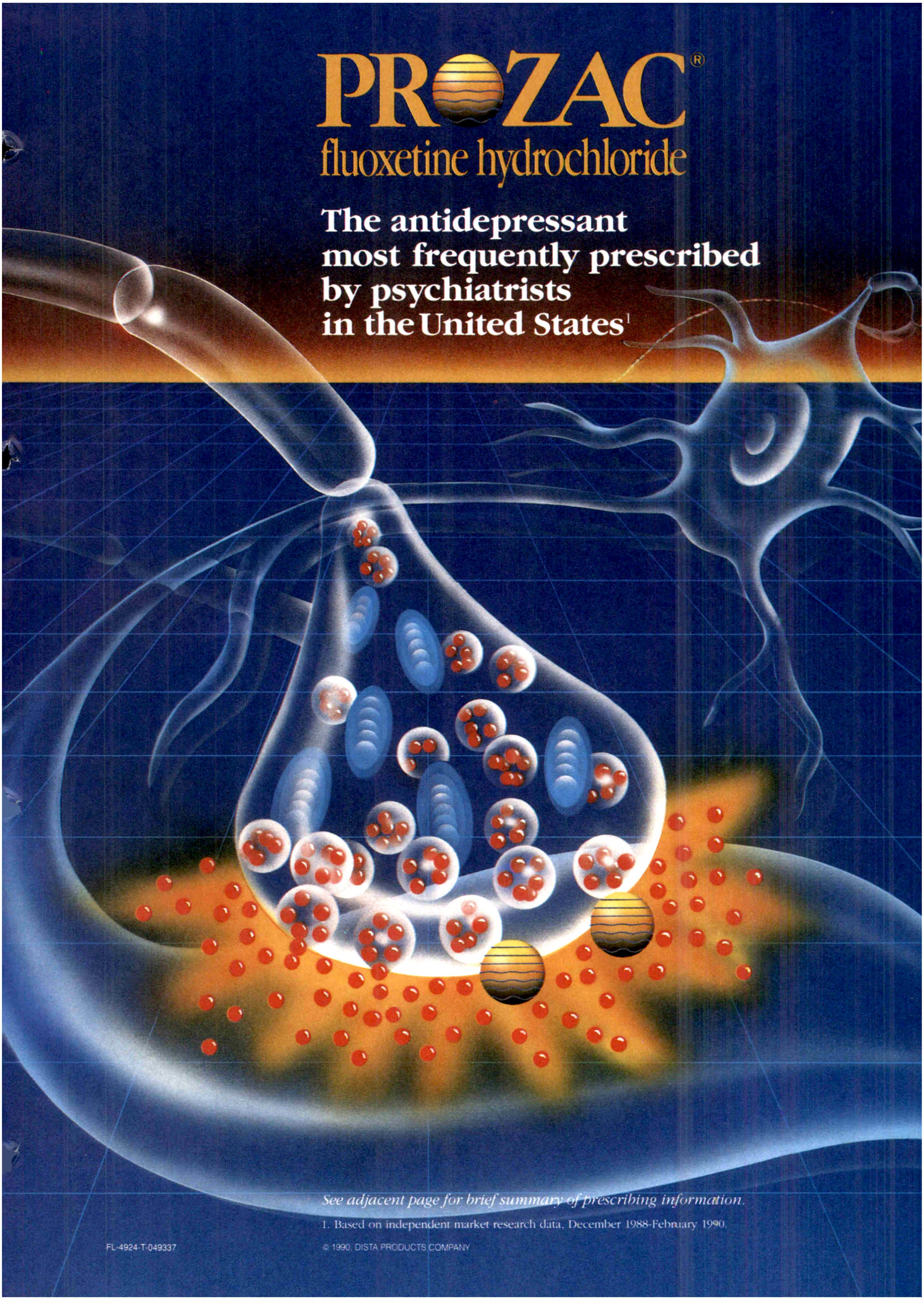

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most frequently prescribed
by psychiatrists
in the United States[1]

See adjacent page for brief summary of prescribing information.

1. Based on independent market research data, December 1988-February 1990.

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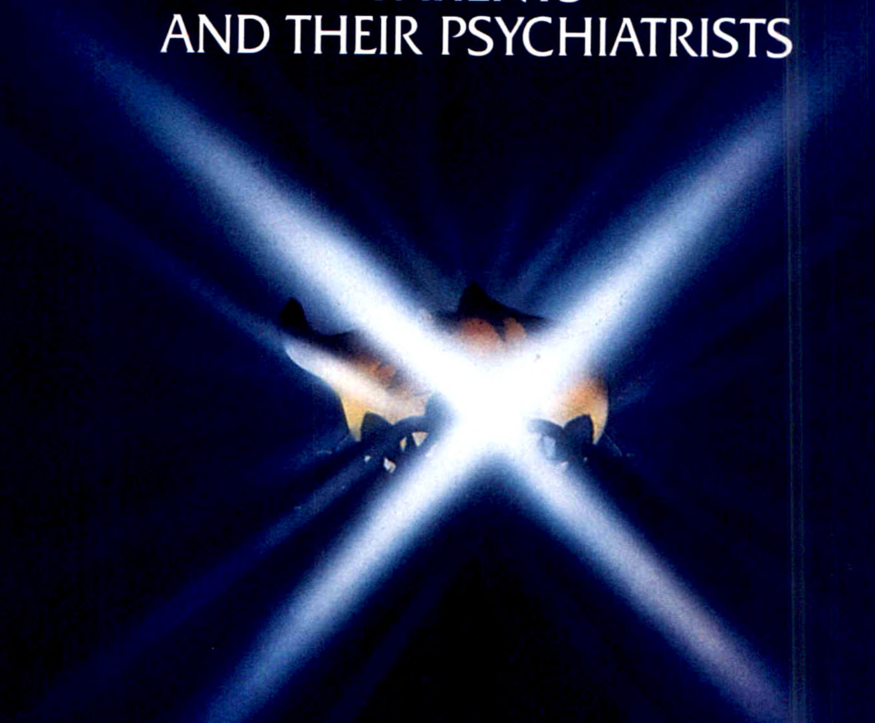
OF PROBLEM SCHIZOPHRENIC
PATIENTS
AND THEIR PSYCHIATRISTS



HOPE BEGINS WITH SUPERIOR SYMPTOMATIC CONTROL*

In a six-week controlled study in severely ill ("problem") schizophrenic patients who failed to respond adequately to treatment with appropriate courses of standard antipsychotic drugs:

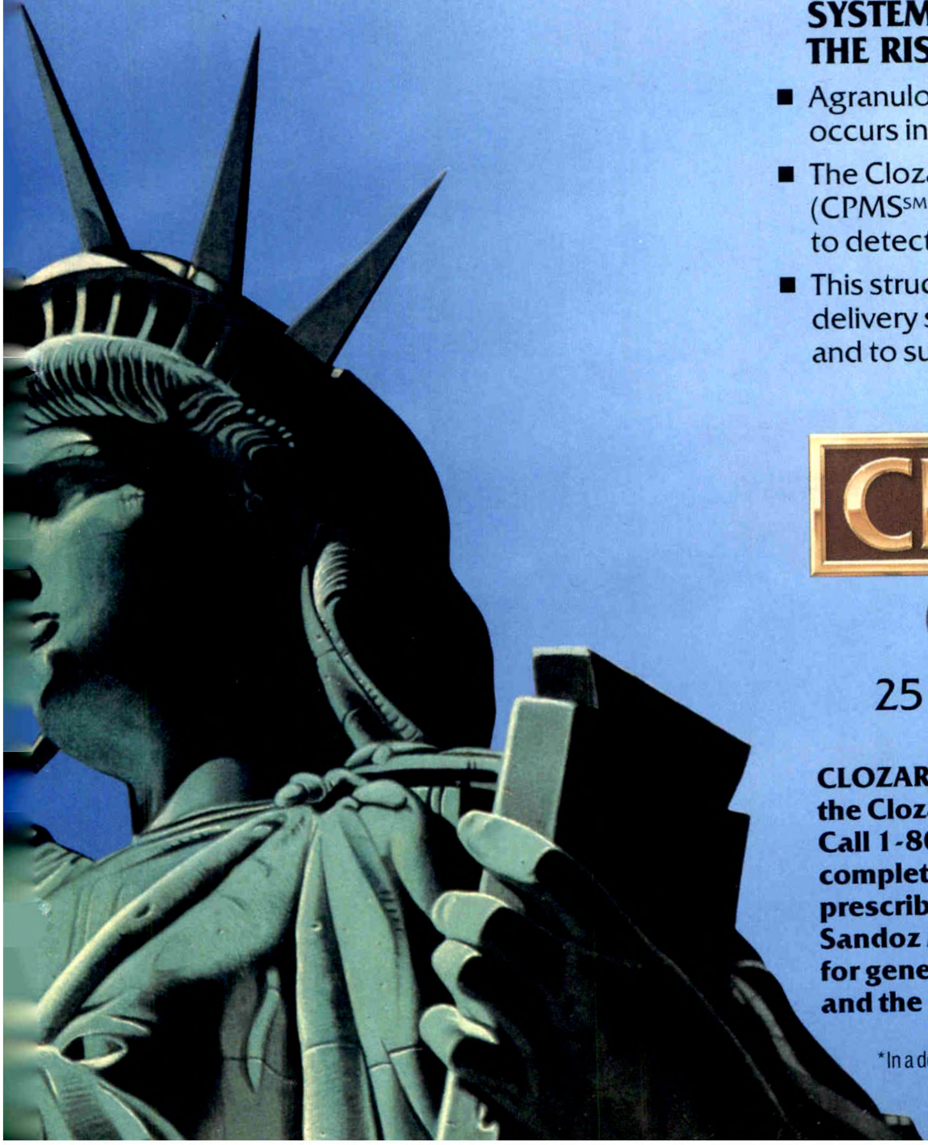
- CLOZARIL® (clozapine) succeeded after standard antipsychotics, including haloperidol, failed
- Thirty percent of CLOZARIL patients experienced dramatic global improvement in only six weeks (as determined by the study's rigorous efficacy criteria) vs only 4% of patients receiving chlorpromazine
- Efficacy in both positive and negative symptomatology

HOPE CONTINUES WITH A VIRTUAL ABSENCE OF CERTAIN ACUTE EXTRAPYRAMIDAL SYMPTOMS

- CLOZARIL® (clozapine) is indicated for patients intolerant of standard antipsychotics
- No confirmed cases of tardive dyskinesia in over 15 years' worldwide experience
- Side effects that have been reported include: agranulocytosis (1–2%), transient sedation (39%), hypersalivation (31%), tachycardia (25%), constipation (14%), hypotension (9%), hypertension (4%) and weight gain (4%)[†]
- CLOZARIL use is associated with a substantial risk of seizure, an apparently dose-dependent reaction affecting 1–2% of patients at low doses (below 300 mg/day), 3–4% at moderate doses, and 5% at high doses (600–900 mg/day)[‡]

HOPE IS MAINTAINED THROUGH A MANDATORY WBC MONITORING SYSTEM WHICH HELPS MANAGE THE RISK OF AGRANULOCYTOSIS

- Agranulocytosis, a potentially fatal disorder, occurs in 1–2% of patients
- The Clozaril Patient Management System℠ (CPMS℠) was created as an efficient means to detect developing agranulocytosis
- This structured weekly monitoring and drug delivery system helps to protect the patient and to support the physician



CLOZARIL®

(clozapine)

25 mg and 100 mg tablets

CLOZARIL therapy is available only through the Clozaril Patient Management System. Call 1-800-237-CPMS (2767) or mail in a completed CPMS patient enrollment form to prescribe CLOZARIL (clozapine). Contact your Sandoz Mental Health Sales Representative for general information on CLOZARIL (clozapine) and the Clozaril Patient Management System.

*In a double-blind study of CLOZARIL (clozapine) versus chlorpromazine encompassing 268 patients, all of whom had first failed on at least three standard antipsychotics over a five-year period and then on a trial of high-dose haloperidol.

CLOZARIL®

(clozapine)

TABLETS

CAUTION: Federal law prohibits dispensing without a prescription.

CONTRAINDICATIONS

CLOZARIL is contraindicated in patients with myeloproliferative disorders, or a history of CLOZARIL-induced agranulocytosis or severe granulocytopenia. CLOZARIL should not be used simultaneously with other agents having a well-known potential to suppress bone marrow function. As with more typical antipsychotic drugs, CLOZARIL is contraindicated in severe central nervous system depression or comatose states from any cause.

WARNINGS

General

BECAUSE OF THE SIGNIFICANT RISK OF AGRANULOCYTOSIS, A POTENTIALLY LIFE-THREATENING ADVERSE EVENT (SEE BELOW), CLOZARIL SHOULD BE RESERVED FOR USE IN THE TREATMENT OF SEVERELY ILL SCHIZOPHRENIC PATIENTS WHO FAIL TO SHOW AN ACCEPTABLE RESPONSE TO ADEQUATE COURSES OF STANDARD ANTIPSYCHOTIC DRUG TREATMENT, EITHER BECAUSE OF INSUFFICIENT EFFECTIVENESS OR THE INABILITY TO ACHIEVE AN EFFECTIVE DOSE DUE TO INTOLERABLE ADVERSE EFFECTS FROM THOSE DRUGS. CONSEQUENTLY, BEFORE INITIATING TREATMENT WITH CLOZARIL, IT IS STRONGLY RECOMMENDED THAT A PATIENT BE GIVEN AT LEAST TWO TRIALS, EACH WITH A DIFFERENT STANDARD ANTIPSYCHOTIC DRUG PRODUCT, AT AN ADEQUATE DOSE AND FOR AN ADEQUATE DURATION.

PATIENTS WHO ARE BEING TREATED WITH CLOZARIL MUST HAVE A BASELINE WHITE BLOOD CELL (WBC) AND DIFFERENTIAL COUNT BEFORE INITIATION OF TREATMENT, AND A WBC COUNT EVERY WEEK THROUGHOUT TREATMENT, AND FOR FOUR WEEKS AFTER THE DISCONTINUATION OF CLOZARIL.

CLOZARIL IS AVAILABLE ONLY THROUGH THE CLOZARIL PATIENT MANAGEMENT SYSTEM^{SM} (CPMS^{SM}).

Agranulocytosis

Agranulocytosis, defined as a granulocyte count (polys + bands) of less than 500 per mm^3, has been estimated to occur in association with CLOZARIL use at a cumulative incidence at one year of approximately 1.3%, based on the occurrence of 15 U.S. cases out of 1743 patients exposed to CLOZARIL during its clinical testing prior to domestic marketing. All of these cases occurred at a time when the need for close monitoring of WBC counts was already recognized. This reaction could prove fatal if not detected early and therapy interrupted. While no fatalities have been associated with the U.S. agranulocytosis cases, and all cases have recovered fully, the U.S. sample is too small to reliably estimate the case fatality rate. Of the 112 cases of agranulocytosis reported worldwide in association with CLOZARIL use as of December 31, 1986, 35% were fatal. However, few of these deaths occurred since 1977, at which time the knowledge of CLOZARIL-induced agranulocytosis became more widespread, and close monitoring of WBC counts more widely practiced. Nevertheless, it is unknown at present what the case fatality rate will be for CLOZARIL-induced agranulocytosis, despite strict adherence to the recommendation for weekly monitoring of WBC counts.

Treatment should not be initiated if the WBC count is less than 3500 per mm^3, or if the patient has a history of a myeloproliferative disorder, or previous CLOZARIL-induced agranulocytosis or granulocytopenia. Patients should be advised to report immediately the appearance of lethargy, weakness, fever, sore throat or any other signs of infection. If, after the initiation of treatment, the total WBC count has dropped below 3500 per mm^3 or it has dropped by a substantial amount from baseline, even if the count is above 3500 per mm^3, or if immature forms are present, a repeat WBC count and a differential count should be done. If subsequent WBC counts and the differential count reveal a total WBC count between 3000 and 3500 per mm^3 and a granulocyte count above 1500 per mm^3, twice weekly WBC counts and differential counts should be performed.

If the total WBC count falls below 3000 per mm^3 or the granulocyte count below 1500 per mm^3, CLOZARIL therapy should be interrupted and patients should be carefully monitored for flu-like symptoms or other symptoms suggestive of infection. CLOZARIL therapy may be resumed if no symptoms of infection develop, and if the total WBC count returns to levels above 3000 per mm^3 and the granulocyte count returns to levels above 1500 per mm^3. However, in this event, twice-weekly WBC counts and differential counts should continue until total WBC counts return to levels above 3500 per mm^3.

If the total WBC count falls below 2000 per mm^3 or the granulocyte count falls below 1000 per mm^3, bone marrow aspiration should be considered to ascertain granulopoietic status. Protective isolation with close observation may be indicated if granulopoiesis is determined to be deficient. Should evidence of infection develop, the patient should have appropriate cultures performed and an appropriate antibiotic regimen instituted.

Patients whose total WBC counts fall below 2000 per mm^3, or granulocyte counts below 1000 per mm^3 during CLOZARIL therapy should *not* be re-challenged with CLOZARIL. Patients discontinued from CLOZARIL therapy due to significant WBC suppression have been found to develop agranulocytosis upon re-challenge, often with a shorter latency on re-exposure. To reduce the chances of re-challenge occurring in patients who have experienced significant bone marrow suppression during CLOZARIL therapy, a single, national master file will be maintained confidentially within the CPMS (Clozaril Patient Management System).

Except for evidence of significant bone marrow suppression during initial CLOZARIL therapy, there are no established risk factors, based on worldwide experience, for the development of agranulocytosis in association with CLOZARIL use. However, a disproportionate number of the U.S. cases of agranulocytosis occurred in patients of Jewish background compared to the overall proportion of such patients exposed during the domestic development of CLOZARIL. Most of the U.S. cases occurred within 4-10 weeks of exposure, but neither dose nor duration is a reliable predictor of this problem. No patient characteristics have been clearly linked to the development of agranulocytosis in association with CLOZARIL use, but agranulocytosis associated with other antipsychotic drugs has been reported to occur with a greater frequency in women, the elderly and in patients who are cachectic or have serious underlying medical illness; such patients may also be at particular risk with CLOZARIL.

To reduce the risk of agranulocytosis developing undetected, CLOZARIL will be dispensed only within the Clozaril Patient Management System.

Seizures

Seizure has been estimated to occur in association with CLOZARIL use at a cumulative incidence at one year of approximately 5%, based on the occurrence of one or more seizures in 61 of 1743 patients exposed to CLOZARIL during its clinical testing prior to domestic marketing (i.e., a crude rate of 3.5%). Dose appears to be an important predictor of seizure, with a greater likelihood of seizure at the higher CLOZARIL doses used.

Caution should be used in administering CLOZARIL to patients having a history of seizures or other predisposing factors. Because of the substantial risk of seizure associated with CLOZARIL use, patients should be advised not to engage in any activity where sudden loss of consciousness could cause serious risk to themselves or others, e.g., the operation of complex machinery, driving an automobile, swimming, climbing, etc.

Adverse Cardiovascular Effects

Orthostatic hypotension can occur with CLOZARIL treatment, especially during initial titration in association with rapid dose escalation, and may represent a continuing risk in some patients. Tachycardia, which may be sustained, has also been observed in approximately 25% of patients taking CLOZARIL, with patients having an average increase in pulse rate of 10-15 bpm. The sustained tachycardia is not simply a reflex response to hypotension, and is present in all positions monitored. Either tachycardia or hypotension may pose a serious risk for an individual with compromised cardiovascular function. A minority of CLOZARIL-treated patients experience ECG repolarization changes similar to those seen with other antipsychotic drugs, including S-T segment depression and flattening or inversion of T waves, which all normalize after discontinuation of CLOZARIL. The clinical significance of these changes is unclear. However, in clinical trials with CLOZARIL, several patients experienced significant cardiac events, including ischemic changes, myocardial infarction, nonfatal arrhythmias and sudden unexplained death. Causality assessment was difficult in many of these cases because of serious preexisting cardiac disease and plausible alternative causes. Rare instances of sudden, unexplained death have been reported in psychiatric patients, with or without associated antipsychotic drug treatment, and the relationship of these events to antipsychotic drug use is unknown. CLOZARIL should be used with caution in patients with known cardiovascular disease, and the recommendation for gradual titration of dose should be carefully observed.

Neuroleptic Malignant Syndrome

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). No cases of NMS have been attributed to CLOZARIL alone. However, there have been several reported cases of NMS in patients treated concomitantly with lithium or other CNS-active agents.

Tardive Dyskinesia

A syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of treatment, which patients are likely to develop the syndrome.

There are several reasons for predicting that CLOZARIL may be different from other antipsychotic drugs in its potential for inducing tardive dyskinesia, including the preclinical finding that it has a relatively weak dopamine blocking effect and the clinical finding of a virtual absence of certain acute extrapyramidal symptoms, e.g., dystonia. In addition, there have been no confirmed cases of tardive dyskinesia developing in association with CLOZARIL use. Nevertheless, it cannot yet be concluded, without more extended experience, that CLOZARIL is incapable of inducing this syndrome.

PRECAUTIONS

Because of the significant risk of agranulocytosis and seizure, both of which present a continuing risk over time, the extended treatment of patients failing to show an acceptable level of clinical response should ordinarily be avoided. In addition, the need for continuing treatment in patients exhibiting beneficial clinical responses should be periodically re-evaluated. During CLOZARIL therapy, patients may experience transient temperature elevations above 100.4°F (38°C), with the peak incidence within the first three weeks of treatment. While this fever is generally benign and self-limiting, it may necessitate discontinuing patients from treatment. On occasion, there may be an associated increase or decrease in WBC count. Patients with fever should be carefully evaluated to rule out the possibility of an underlying infectious process or the development of agranulocytosis. In the presence of high fever, the possibility of neuroleptic malignant syndrome (NMS) must be considered. CLOZARIL has very potent anticholinergic effects, and great care should be exercised in using this drug in the presence of prostatic enlargement or narrow angle glaucoma. Because of initial sedation, CLOZARIL may impair mental and/or physical abilities, especially during the first few days of therapy. The recommendations for gradual dose escalation should be carefully adhered to, and patients cautioned about activities requiring alertness. Clinical experience with CLOZARIL in patients with concomitant systemic diseases is limited. Nevertheless, caution is advisable in using CLOZARIL in patients with hepatic, renal or cardiac disease.

Information for Patients

Patients who are to receive CLOZARIL should be warned about the significant risk of developing agranulocytosis. They should be informed that weekly blood tests are required to monitor for the occurrence of agranulocytosis, and that CLOZARIL tablets will be made available only through a special program designed to ensure the required blood monitoring. Patients should be advised to report immediately the appearance of lethargy, weakness, fever, sore throat, malaise, mucous membrane ulceration or other possible signs of infection. Particular attention should be paid to any flu-like complaints or other symptoms that might suggest infection. Patients should be informed of the significant risk of seizure during CLOZARIL treatment, and they should be advised to avoid driving and any other potentially hazardous activity while taking CLOZARIL. Patients should be advised of the risk of orthostatic hypotension, especially during the period of initial dose titration. Patients should notify their physician if they are taking, or plan to take, any prescription or over-the-counter drugs or alcohol. Patients should notify their physician if they become pregnant or intend to become pregnant during therapy. Patients should not breast feed an infant if they are taking CLOZARIL.

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TABLETS

Drug Interactions

The risks of using CLOZARIL in combination with other drugs have not been systematically evaluated. The mechanism of CLOZARIL-induced agranulocytosis is unknown; nonetheless, the possibility that causative factors may interact synergistically to increase the risk and/or severity of bone marrow suppression warrants consideration. Therefore CLOZARIL should not be used with other agents having a well-known potential to suppress bone marrow function. Given the primary CNS effects of CLOZARIL, caution is advised in using it concomitantly with other CNS-active drugs. Because CLOZARIL is highly bound to serum protein, the administration of CLOZARIL to a patient taking another drug which is highly bound to protein (e.g., warfarin, digoxin) may cause an increase in plasma concentrations of these drugs, potentially resulting in adverse effects. Conversely, adverse effects may result from displacement of protein-bound CLOZARIL by other highly bound drugs.

CLOZARIL may also potentiate the hypotensive effects of antihypertensive drugs and the anticholinergic effects of atropine-type drugs. The administration of epinephrine should be avoided in the treatment of drug-induced hypotension because of a possible reverse epinephrine effect.

Pregnancy Category B

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, and in view of the desirability of keeping the administration of all drugs to a minimum during pregnancy, this drug should be used only if clearly needed.

ADVERSE REACTIONS

Adverse events observed in association with the use of CLOZARIL in clinical trials at an incidence of 5% or greater were: central nervous system complaints, including drowsiness/sedation, dizziness/vertigo, headache and tremor; autonomic nervous system complaints, including salivation, sweating, dry mouth and visual disturbances; cardiovascular findings, including tachycardia, hypotension and syncope; and gastrointestinal complaints, including constipation and nausea; and fever. Complaints of drowsiness/sedation tend to subside with continued therapy or dose reduction. Salivation may be profuse, especially during sleep, but may be diminished with dose reduction.

DOSAGE AND ADMINISTRATION

Initial Treatment

It is recommended that treatment with CLOZARIL begin at 25 mg once or twice daily, and then be continued with daily dosage increments of 25 to 50 mg/day, if well-tolerated, to achieve a target dose of 300 to 450 mg/day by the end of two weeks. Subsequent dosage increments should be made no more than once- or twice-weekly, in increments not to exceed 100 mg. Cautious titration and a divided dosage schedule are necessary to minimize the risks of hypotension, seizure, and sedation.

Therapeutic Dose Adjustment

Daily dosing should continue on a divided basis as an effective and tolerable dose level is sought. While many patients may respond adequately at doses between 300-600 mg/day, it may be necessary to raise the dose to the 600-900 mg/day range to obtain an acceptable response. [Note: In the multicenter study providing the primary support for the superiority of CLOZARIL in treatment resistant patients, the mean and median CLOZARIL doses were both approximately 600 mg/day.]

Because of the possibility of increased adverse reactions at higher doses, particularly seizures, patients should ordinarily be given adequate time to respond to a given dose level before escalation to a higher dose is contemplated.

Dosing should not exceed 900 mg/day.

Discontinuation of Treatment

In the event of planned termination of CLOZARIL therapy, gradual reduction in dose is recommended over a 1 to 2 week period. However, should a patient's medical condition require abrupt discontinuation (e.g., leukopenia), the patient should be carefully observed for the recurrence of psychotic symptoms.

CLOZARIL is available only through the Clozaril Patient Management System, a program that combines white blood cell testing, patient monitoring, pharmacy, and drug distribution services, all linked to compliance with required safety monitoring.

To prescribe CLOZARIL call 1-800-237-CPMS (2767) or mail in a completed CPMS Enrollment Form.

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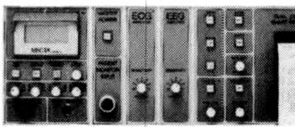

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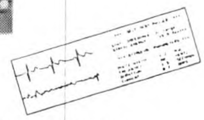

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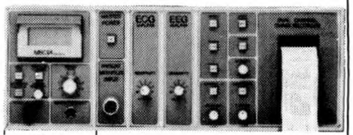

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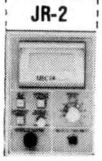

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For further information about the Program for Minority Research Training in Psychiatry, call or write Harold Alan Pincus, M.D., or Jeanne Spurlock, M.D., at the American Psychiatric Association, 1400 K Street, N.W., Washington, D.C. 20005; Telephone 202-682-6238; or FAX 202-682-6114.

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These are usually overview articles that bring together important information on a topic of general interest to psychiatry. Authors who have ideas for such articles are advised to check with the Editorial Office to ensure that a similar work has not already been submitted. Special Articles may not exceed 7,500 words (no more than 25 double-spaced pages—including an abstract of no more than 100 words, tables, and figures) and may not include more than 100 references.

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2. Kaplan HI, Sadock BJ (eds): Comprehensive Textbook of Psychiatry, 4th ed, vol 2. Baltimore, Williams & Wilkins, 1985
3. Fyer AJ, Manuzza S, Endicott J: Differential diagnosis and assessments of anxiety: recent developments, in Psychopharmacology: The Third Generation of Progress. Edited by Meltzer HY. New York, Raven Press, 1987

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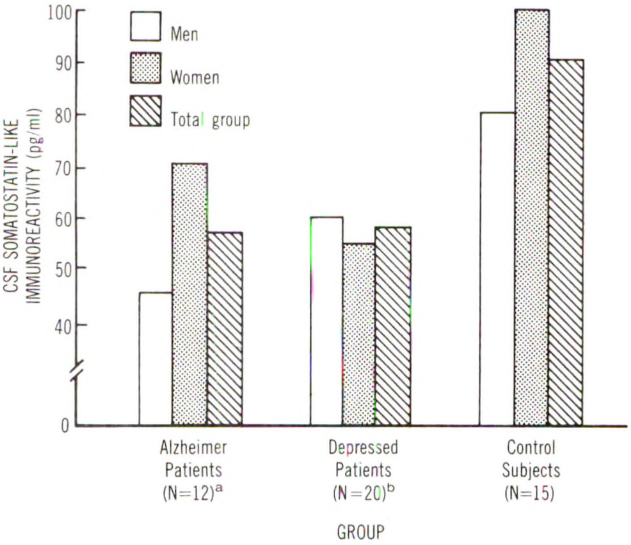
FIGURE 1. Mean CSF Somatostatin Levels of Patients With Alzheimer's Disease, Older Depressed Patients, and Age-Matched Control Subjects



[a] Significant difference between men and women ($t=1.81$, $df=10$, $p<0.05$) and between the total Alzheimer's disease group and the total control group ($t=2.49$, $df=25$, $p<0.01$).

[b] Significant difference between the total depressed group and the total control group ($t=2.75$, $df=33$, $p<0.005$).

cient, headings may be placed diagonally on the axis. Main headings should consist of upper-case letters only, subheadings of upper- and lower-case, and other type (e.g., keys, flow chart segments) of lower-case with only an initial upper-case letter. All parenthetical material should be lower-case. Do not use idiosyncratic abbreviations.

Other. The following are additional specific requirements. Please refer to the example given above.

1. Do not use solid black shading; rather, include outlined white among shadings.
2. The heading for the vertical axis of a graph should run vertically along the axis, not horizontally at the top or bottom. Headings for the horizontal axis should appear below that axis, not at the top of the graph.
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6. In a graph comparing different groups of subjects, the number of subjects in each group should appear with the name of the group—in the key, in the headings below the horizontal axis, or in the title.
7. To save space, related figures that have the same vertical or horizontal axis should be combined. Headings identifying the segments of the combined figure should appear in the upper lefthand corners of the individual segments (in lower-case type with an initial upper-case letter).
8. The key should appear within or above the figure but should not be wider than the figure itself. Avoid placing other type (e.g., number of subjects, statistical values) within the axes of a graph.
9. Footnotes (including p values) should be cited with superscript letters in the title or body of the figure and should be listed in the order in which they are cited in the figure.

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References: **1.** Goldberg HL: Sleep disturbance as a manifestation of depression, in *Somatic Depression: Insights for Primary Care Physicians*. Proceedings of a symposium held in Miami, Dec 4, 1978. New York, Postgraduate Medicine Communications, pp 13-18. **2.** Karacan I, Blackburn AB, Thornby JI, et al: The effect of doxepin HCl (Sinequan) on sleep patterns and clinical symptomatology of neurotic depressed patients with sleep disturbance, in *Sinequan® (doxepin HCl): A Monograph of Recent Clinical Studies*. Princeton, NJ, Excerpta Medica, 1977, pp 4-22. **3.** Goldberg HL, Finnerty RJ: The use of doxepin in the treatment of symptoms of anxiety neurosis and accompanying depression: A collaborative controlled study. *Am J Psychiatry* 1972;129(July) 74-77.

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Usage in Geriatrics: The use of SINEQUAN on a once-a-day dosage regimen in geriatric patients should be adjusted carefully based on the patient's condition.

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Usage in Children: The use of SINEQUAN in children under 12 years of age is not recommended because safe conditions for its use have not been established.

Drug Interactions.

MAO Inhibitors: Serious side effects and even death have been reported following the concomitant use of certain drugs with MAO inhibitors. Therefore, MAO inhibitors should be discontinued at least two weeks prior to the cautious initiation of therapy with SINEQUAN. The exact length of time may vary and is dependent upon the particular MAO inhibitor being used, the length of time it has been administered, and the dosage involved.

Cimetidine: Cimetidine has been reported to produce clinically significant fluctuations in steady-state serum concentrations of various tricyclic antidepressants. Serious anticholinergic symptoms (i.e., severe dry mouth, urinary retention and blurred vision) have been associated with elevations in the serum levels of tricyclic antidepressant when cimetidine therapy is initiated. Additionally, higher than expected tricyclic antidepressant levels have been observed when they are begun in patients already taking cimetidine. In patients who have been reported to be well controlled on tricyclic antidepressants receiving concurrent cimetidine therapy, discontinuation of cimetidine has been reported to decrease established steady-state serum tricyclic antidepressant levels and compromise their therapeutic effects.

Alcohol: It should be borne in mind that alcohol ingestion may increase the danger inherent in any intentional or unintentional SINEQUAN overdosage. This is especially important in patients who may use alcohol excessively.

Tolazamide: A case of severe hypoglycemia has been reported in a type II diabetic patient maintained on tolazamide (1 gm/day) 11 days after the addition of doxepin (75 mg/day).

Precautions. Since drowsiness may occur with the use of this drug, patients should be warned of the possibility and cautioned against driving a car or operating dangerous machinery while taking the drug. Patients should also be cautioned that their response to alcohol may be potentiated.

Since suicide is an inherent risk in any depressed patient and may remain so until significant improvement has occurred, patients should be closely supervised during the early course of therapy. Prescriptions should be written for the smallest feasible amount.

Should increased symptoms of psychosis or shift to manic symptomatology occur, it may be necessary to reduce dosage or add a major tranquilizer to the dosage regimen.

Adverse Reactions. NOTE: Some of the adverse reactions noted below have not been specifically reported with SINEQUAN use. However, due to the close pharmacological similarities among the tricyclics, the reactions should be considered when prescribing SINEQUAN (doxepin HCl).

Anticholinergic Effects: Dry mouth, blurred vision, constipation, and urinary retention have been reported. If they do not subside with continued therapy, or become severe, it may be necessary to reduce the dosage.

Central Nervous System Effects: Drowsiness is the most commonly noticed side effect. This tends to disappear as therapy is continued. Other infrequently reported CNS side effects are confusion, disorientation, hallucinations, numbness, paresthesias, ataxia, extrapyramidal symptoms, seizures, tardive dyskinesia, and tremor.

Cardiovascular: Cardiovascular effects including hypotension, hypertension, and tachycardia have been reported occasionally.

Allergic: Skin rash, edema, photosensitization, and pruritus have occasionally occurred.

Hematologic: Eosinophilia has been reported in a few patients. There have been occasional reports of bone marrow depression manifesting as agranulocytosis, leukopenia, thrombocytopenia, and purpura.

Gastrointestinal: Nausea, vomiting, indigestion, taste disturbances, diarrhea, anorexia, and aphthous stomatitis have been reported. (See anticholinergic effects.)

Endocrine: Raised or lowered libido, testicular swelling, gynecomastia in males, enlargement of breasts and galactorrhea in the female, raising or lowering of blood sugar levels, and syndrome of inappropriate antidiuretic hormone secretion have been reported with tricyclic administration.

Other: Dizziness, tinnitus, weight gain, sweating, chills, fatigue, weakness, flushing, jaundice, alopecia, headache, exacerbation of asthma, and hyperpyrexia (in association with chlorpromazine) have been occasionally observed as adverse effects.

Withdrawal Symptoms: The possibility of development of withdrawal symptoms upon abrupt cessation of treatment after prolonged SINEQUAN administration should be borne in mind. These are not indicative of addiction and gradual withdrawal of medication should not cause these symptoms.

Dosage and Administration. For most patients with illness of mild to moderate severity, a starting daily dose of 75 mg is recommended. Dosage may subsequently be increased or decreased at appropriate intervals and according to individual response. The usual optimum dose range is 75 mg/day to 150 mg/day.

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Anti-anxiety effect is apparent before the antidepressant effect. Optimal antidepressant effect may not be evident for two to three weeks.

Overdosage.

A. Signs and Symptoms
  1. Mild: Drowsiness, stupor, blurred vision, excessive dryness of mouth.
  2. Severe: Respiratory depression, hypotension, coma, convulsions, cardiac arrhythmias and tachycardias.

Also: urinary retention (bladder atony), decreased gastrointestinal motility (paralytic ileus), hyperthermia (or hypothermia), hypertension, dilated pupils, hyperactive reflexes.

B. Management and Treatment
  1. Mild: Observation and supportive therapy is all that is usually necessary.
  2. Severe: Medical management of severe SINEQUAN overdosage consists of aggressive supportive therapy. If the patient is conscious, gastric lavage, with appropriate precautions to prevent pulmonary aspiration, should be performed even though SINEQUAN is rapidly absorbed. The use of activated charcoal has been recommended, as has been continuous gastric lavage with saline for 24 hours or more. An adequate airway should be established in comatose patients and assisted ventilation used if necessary. EKG monitoring may be required for several days, since relapse after apparent recovery has been reported. Arrhythmias should be treated with the appropriate antiarrhythmic agent. It has been reported that many of the cardiovascular and CNS symptoms of tricyclic antidepressant poisoning in adults may be reversed by the slow intravenous administration of 1 mg to 3 mg of physostigmine salicylate. Because physostigmine is rapidly metabolized, the dosage should be repeated as required. Convulsions may respond to standard anticonvulsant therapy, however, barbiturates may potentiate any respiratory depression. Dialysis and forced diuresis generally are not of value in the management of overdosage due to high tissue and protein binding of SINEQUAN.

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The American Psychiatric Association takes pleasure in inviting submissions for the fourteenth annual Foundations' Fund Prize for Research in Psychiatry.

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The sponsor should submit a supporting letter (six copies) setting out in detail justification for a nomination and summarizing the research accomplishments of the nominee in a specific area or with a coherent theme.

The nominee should submit:

(A) A book or paper (six copies, or a group of representative and thematically linked, books or papers (six copies) published in English (or accepted for publication) and dates within ten years prior to the deadline of submission.

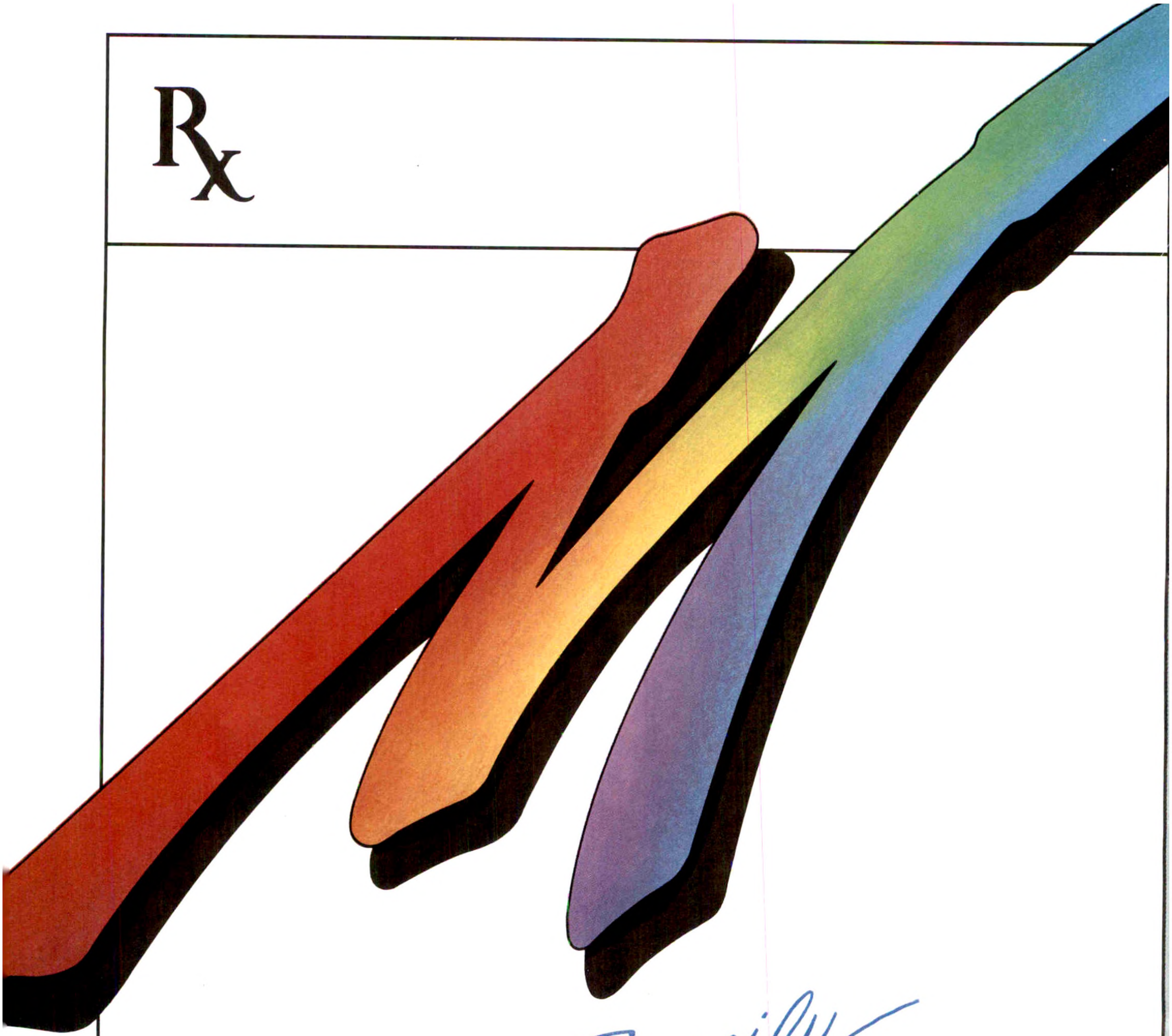
(B) A summary statement (six copies) written by the nominee, emphasizing the principal theme running through their work, its internal cohesiveness and consistency, and scientific implications.

(C) An up-to-date curriculum vitae (six copies)

(D) An up-to-date bibliography (six copies)

All entries must be submitted in six complete collated sets and sent to Ira D. Glick, M.D., Chairman, Foundations' Fund Prize Board for Research in Psychiatry, American Psychiatric Association, 1400 K St., N.W., Washington, D.C. 20005. Entries will be acknowledged but cannot be returned. The prize is based on a yearly competition. Resubmission is permitted. The award will be presented at the convocation of fellows at the Association's Annual Meeting in May of 1991.

The deadline for submission is January 1, 1991.



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THE AMERICAN JOURNAL OF PSYCHIATRY
Special Articles

DSM-IV: Work in Progress

Allen Frances, M.D., Harold Alan Pincus, M.D., Thomas A. Widiger, Ph.D., Wendy Wakefield Davis, M.Ed., and Michael B. First, M.D.

The authors present an overview of the work in progress on DSM-IV. *After a brief historical review, they discuss the principles and multiple purposes of the* DSM-IV *effort and outline the three stages of its empirical documentation: systematic literature reviews, analysis of unpublished data, and field trials. Next, they discuss several of the basic conceptual issues that are implicit in revising a nomenclature. These include the definition of mental disorder, the balance between multiple diagnosis and differential diagnosis, the use of categorical and dimensional models of classification, and issues involved in the construction of criteria. Finally, they summarize the most important specific questions being reviewed by each of the* DSM-IV *work groups.*

(Am J Psychiatry 1990; 147:1439–1448)

There was a paradigm shift in *DSM-III* (1, 2) toward descriptive psychiatric diagnosis that was meant to be neutral with regard to etiology and usable across theoretical orientations (3, 4). Two methodological innovations—explicit diagnostic criteria and the multiaxial system—improved on the poor reliability achieved by previous systems and facilitated clinical communication and research. The manual has been widely used by clinicians, educators, trainees, and researchers. *DSM-III* was both a reflection of and a catalyst for the increased emphasis on empirical data in psychiatric practice and research.

Despite its important contributions, *DSM-III* was by no means universally popular or without disadvantages (5–13). Perhaps the most serious problem was not inherent in the content of the manual but resulted from how it was viewed and used. Many persons reified the criteria in *DSM-III* despite the fact that most were based on expert opinion rather than systematic evidence. The criteria were meant to guide clinical practice rather than subject it to rigid rules. A second limitation of *DSM-III* was its length and cumbersomeness. It also stirred numerous controversies. Some of these concerned the definition of particular diagnoses; others related more generally to professional, forensic, economic, or social consequences of the system.

Work on a revision of *DSM-III* began in 1983 and resulted in publication of *DSM-III-R* in 1987. *DSM-III-R* was undertaken in order to correct inconsistencies identified after the publication of *DSM-III* and to allow for the inclusion of new evidence (14). The revision of *DSM-III* was probably more substantial than had originally been anticipated. Although *DSM-III-R* was useful in demonstrating that the system is self-correcting, it may have been too big a change too soon, with consequent disruption to clinical, research, and educational endeavors (15–19).

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The authors thank the members of the APA Task Force on *DSM-IV:* Nancy C. Andreasen, M.D., Ph.D.; Magda Campbell, M.D.; Dennis Cantwell, M.D.; Junius Gonzales, M.D.; John Gunderson, M.D.; Judith Gold, M.D.; Robert Hales, M.D.; Kenneth Kendler, M.D.; David Kupfer, M.D.; Michael Liebowitz, M.D.; Juan Mezzich, M.D.; Roger Peele, M.D.; Darrel Regier, M.D.; A. John Rush, M.D.; Marc Schuckit, M.D.; Chester Schmidt, M.D.; David Shaffer, M.D.; Robert L. Spitzer, M.D.; Gary Tucker, M.D.; B. Timothy Walsh, M.D.; and Janet B.W. Williams, D.S.W. They also thank Gloria M. Miele, M.A., and Sarah M. Tilly, M.A., of the *DSM-IV* staff.

The opinions expressed in this paper are those of the authors and do not necessarily represent the position of the American Psychiatric Association and its Task Force on *DSM-IV*.

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In May 1988, the Board of Trustees of the American Psychiatric Association (APA) appointed a task force to begin work on *DSM-IV*. Elsewhere we have indicated the considerations that led to this decision (20). The major reason to begin work so soon in preparation for *DSM-IV* was the expected publication of the tenth edition of the *International Classification of Diseases* (*ICD-10*) in 1993. Early drafts of the Mental Disorders section of *ICD-10* were quite different from that of *ICD-9* and from *DSM-III-R* (and actually more like *DSM-III*). Since the United States is obliged to use *ICD* codes, and since it is highly desirable to eliminate unnecessary differences between systems, it seemed crucial for the groups working on *DSM-IV* and *ICD-10* to have an opportunity for discussion and mutual influence (1, 21). Indeed, the appointment of the Task Force on *DSM-IV* was done with this in mind, and repeated consultations have resulted in greatly increased compatibility between systems.

The purpose of this article is to discuss issues involved in the preparation of *DSM-IV*. We begin with a brief review of historical trends in psychiatric diagnosis in order to place current efforts in context. Next, we outline the multiple purposes of *DSM-IV* and ways in which these must be balanced. We then discuss several of the difficult conceptual issues that are implicit in revising a nomenclature. Finally, we summarize the most important specific questions being reviewed by each of the *DSM-IV* work groups.

HISTORICAL REVIEW

Although the need for a classification of mental disorders has been clear throughout the history of medicine, there has been controversy on optimal methods and content. Psychiatric nomenclatures have differed with respect to their relative emphasis on phenomenology, etiology, and course as defining features.

A classification developed in ancient Greece and Rome distinguished five categories defined by their phenomenology: phrenitis, mania, melancholia, hysteria, and epilepsy. The ancient Greek version of axis II included the four temperaments as described by Hippocrates: choleric, sanguine, melancholic, and phlegmatic.

In the sixteenth century the Swiss physician Paracelsus developed a classification based on etiology: vesania (disorders caused by poisons), lunacy (a periodic condition influenced by phases of the moon), and insanity (diseases caused by heredity).

Influenced by the work of Linnaeus and Sydenham, Boissier de Sauvages argued that classification should be based on the distinguishing symptoms, with causal theory excluded (22). His taxonomy arranged symptoms into classes, orders, and genera, comparable to zoological classifications, and generated 2,400 mental disorders, each of which was essentially a symptom. Psychiatric classification has struggled ever since with the conflicting demands of theoretically simple, descriptive systems that generate a large number of narrowly defined conditions versus systems that have organizing theoretical emphases and smaller numbers of groupings.

Esquirol emphasized age at onset and course of illness as valuable additions to cross-sectional descriptive definition. This approach was incorporated into Morel's nineteenth-century diagnosis of *démence précoce*. Kraepelin's combination of descriptive phenomenology and course (22, 23) provided the basic conceptual framework for *DSM-III*. *DSM-III* placed less emphasis than had *DSM-I* and *DSM-II* on other trends in twentieth-century nosology, e.g., Bleuler's more cross-sectional assessment of fundamental features of schizophrenia, Meyer's psychobiological "reaction sets" to environmental stressors, and Freud's description of mental mechanisms.

The ancestors of *DSM-IV* also arose from the need to develop systems for statistical, epidemiological, and reporting purposes. In 1840 the U.S. census had but one category for mental disorder. The 1880 census expanded to seven categories (mania, melancholia, monomania, paresis, dementia, dipsomania, and epilepsy). In 1917 APA adopted a classification of mental diseases to obtain uniform statistics in hospitals (24, 25). Because this had only limited value as a general nomenclature, it was replaced by the American Medical Association's *Standard Classified Nomenclature of Disease* (26), which contained 24 major categories much influenced by the sixth edition of Kraepelin's textbook (24). Because previous classifications designed primarily for inpatients were inadequate during World War II, the U.S. armed forces developed a new system, which was later revised for use by the Veterans Administration. The World Health Organization (WHO) published its first international classification of mental disorders, *ICD-6*, in 1948 (27).

The variety of nomenclatures was confusing. Some agencies used one system for clinical use, another for disability ratings, and a third for statistical reporting. *DSM-I* provided a uniform system for use in diverse settings that was appropriate for both diagnostic and statistical purposes and included a glossary of definitions of the categories (24, 25). Because the situation internationally was as inconsistent as it had been in America prior to *DSM-I*, WHO sponsored a revision that appeared as *ICD-8* in 1968. APA contributed to *ICD-8* and also published a compatible *DSM-II* simultaneously. Then, in 1980, *DSM-III* and *ICD-9* were published simultaneously, and in a fashion that permitted crosswalking.

PRINCIPLES AND PURPOSES OF *DSM-IV*

Focus on Empirical Documentation

The major innovation of *DSM-IV* is less likely to be any specific content changes than its emphasis on explicit documentation and review of evidence. We have discussed elsewhere the ways in which empirical evidence will be used in preparing *DSM-IV* (20, 28). Data gathering occurs in three related stages: 1) systematic reviews of the published literature, 2) analyses of already-collected but not previously analyzed data, and 3) field trials. The extensive data gathered, reviewed, and interpreted in this three-step process will be summarized in the *DSM-IV Sourcebook*, which will document the basis for whatever changes are made.

The initial task of each of the *DSM-IV* work groups charged with responsibility for specific sections of the manual was to identify the most pertinent questions regarding each diagnosis and to locate the empirical data relevant to their resolution. We sponsored three methods conferences to articulate for all work groups a systematic procedure for finding, extracting, aggregating, and interpreting data in a comprehensive and objective fashion. Holes in the published literature are being filled through the reanalysis of previously collected data that pertain to important questions raised by the initial reviews conducted by the work groups. This work, funded by the John D. and Catherine T. MacArthur Foundation, also allows us to develop and test empirically based criteria.

The *DSM-IV* field trials (funded by the National Institute of Mental Health and by a second grant from the MacArthur Foundation) will help to resolve inconsistencies among *DSM-III*, *DSM-III-R*, *ICD-10*, and suggested *DSM-IV* criteria generated through literature reviews and data reanalyses. The field trial methodology also provides an opportunity to determine how well suggestions for changes derived from clinical research findings apply in clinical practice.

Criteria for Change

Although it is impossible to develop explicit criteria equally applicable to all decisions about change in *DSM-IV*, some principles have emerged. The threshold for making revisions is much higher than it was for *DSM-III* and *DSM-III-R* (20). Decisions must be substantiated by explicit statements of rationale and by the systematic review of relevant empirical data. In order to increase the clinical utility and user friendliness of *DSM-IV*, we will attempt to simplify and explicate it, particularly when this is justified by empirical data. *DSM-IV* seeks to strike an optimal balance with respect to historical tradition (as embodied in *DSM-III* and *DSM-III-R*), compatibility with *ICD-10*, evidence from reviews of the literature, unpublished data, field trials, and consensus of members of mental health professions. The requirement for evidence to support changes will be set high but will vary across disorders, since the quantity and quality of data available to *DSM-III* and *DSM-III-R* varied across disorders. Common sense will also be necessary—major changes solving minor problems will require more evidence than minor changes solving major problems.

Attention to Users

An official nomenclature must be applicable to the widest diversity of settings, purposes, and cases. *DSM-IV* will be used by clinicians and researchers with all the various orientations that inform our field (e.g., biological, psychodynamic, cognitive, behavioral, family/systems). It will be used by psychiatrists, other physicians, psychologists, nurses, social workers, activity and rehabilitation therapists, and all other mental health professionals. *DSM-IV* must be usable across settings: for inpatients and outpatients, in consultation/liaison, in hospitals, in mental health clinics and private practice, in primary care, and in community populations. *DSM-IV* will be used in forensic and disability deliberations and in insurance reimbursement. It will stimulate research and will have an important role in education. *DSM-IV* will also guide the collection of accurate statistics. It is fortunate that *DSM*'s many uses are usually, if not always, quite compatible with one another.

The first priority for any *DSM* is that it be a useful guide to clinical practice. The interest in diagnosis that pervades psychiatric practice attests to the success of *DSM-III-R* in meeting this challenge (29–31). Nonetheless, some aspects of *DSM-III-R* reduce its clinical utility (30, 32–35). Several categories in *DSM-III-R* are too long and complex for use in everyday practice. The work groups are attempting to simplify such categories. Many users of *DSM* object to the rapidly expanding number of categories. While each suggestion for a new category may add clinical refinement, an endless accumulation of marginal new diagnoses makes *DSM* unnecessarily cumbersome.

DSM-III-R has become an important educational tool for teaching psychopathology and for improving the comprehensiveness of the psychiatric interview (30, 36). It can also be used as a psychoeducational tool with patients, who are relieved to learn that their symptom patterns are not unique. Disadvantages of overreliance on *DSM* as an educational tool result from its being taken too literally (8, 16, 37). Trainees may not realize the importance of applying clinical judgment in the diagnostic process, especially for patients who fall between the boundaries of the *DSM* categories. Moreover, psychiatric diagnosis is only one step in the process of evaluating and formulating a clinical problem and is not to be emphasized at the expense of other important steps in treatment planning.

DSM-III has helped to stimulate the active research enterprise that now informs our field (2). The provision of explicit diagnostic criteria was instrumental in the development of structured interviews and systematic assessment. This is a valuable step, but researchers too often limit themselves solely to the criteria included in *DSM* instead of incorporating criteria from other systems (38). Only by comparing the performance of different criteria will research improve the predictive validity of the definitions. Placement in *DSM* should not determine whether or not a disorder is studied and researched.

Before the publication of *DSM-III*, there was concern about its possible impact on a wide variety of issues beyond its clinical, research, educational, and statistical uses (12, 39). Although there is no inherent reason to suppose that the presence of a *DSM* diagnosis should be important in reimbursement and disability decisions, this is nonetheless often the case. Perhaps the arena of greatest possible abuse is the assessment of criminal responsibility, in which the presence of a diagnosable *DSM* disorder should not be regarded as sufficient to confer the sick role. There has been concern that several proposed diagnoses (e.g., late luteal phase dysphoric disorder, self-defeating personality disorder) would have adverse effects on women. It is unclear to what extent the *DSM-IV* task force should be influenced by the effects its decisions might have beyond the immediate clinical domains for which the system is designed (40). To ignore obvious detrimental effects would be irresponsible, but for *DSM-IV* to have credibility as a system of diagnosis, its clinical uses and foundation in research must have priority. It may also be necessary to expand the statement on "Cautions in the Use of DSM-III-R."

Breadth and Quality of Participation

Because *DSM-IV* will be used by a wide range of mental health professionals in a variety of settings, it is crucial that it incorporate the suggestions of as many of these individuals as possible. Each work group has enlisted between 50 and 100 advisors with a variety of professional orientations, representing both research and clinical practice. The task force has also established formal liaisons with the American Psychological Association, the American Psychological Society, the National Association of Social Workers, the American Nursing Association, the American Occupational Therapy Association, and over 60 additional organizations and associations interested in the development of *DSM-IV*. It circulates a semiannual newsletter, the *DSM-IV Update*, to more than 1,000 interested individuals and organizations to summarize progress and discussions within each work group. Representatives of the Task Force on *DSM-IV* present progress reports at APA's annual meetings, the Institutes on Hospital and Community Psychiatry, and other professional meetings. The task force has included critics early in the process to allow their suggestions to have as much impact as possible.

CONCEPTUAL ISSUES

Definition of Mental Disorder

A definition establishing precisely what a mental disorder is would have an important impact on clinical practice, forensic proceedings (41), and decisions about which of the conditions on the border between normality and pathology should be included in *DSM-IV* (42). Unfortunately, no previous definition of illness, disease, or disorder has ever been particularly successful (42–49), and we have no illusions that we can provide a better solution. It seems unlikely that any explicit set of criteria for defining mental disorder will cover all cases or settle boundary questions.

The concept of mental disorder is like other concepts in medicine and science in failing to have a clear and consistent definition (38, 41, 50). Medical illnesses are defined on various levels of abstraction, such as structural pathology (e.g., ulcerative colitis), symptom presentation (e.g., migraine), deviance from a physiological norm (e.g., hypertension), and etiology (e.g., pneumococcal pneumonia). Mental disorders have also been defined by a variety of concepts, such as distress, dyscontrol, disadvantage, disability, inflexibility, irrationality, etiology, and deviation from a statistical norm. Each is a useful indicator for mental disorder, but none is equivalent to the concept, and different situations call for different definitions. The implicit definition of mental disorders and medical disorders—"that which clinicians treat"—is tautological, but other more abstract concepts consistently fail to provide greater explanatory power.

The term "mental disorder" implies an unfortunate distinction between "mental" disorders and "physical" disorders that is a reductionistic anachronism of mind/body dualism. A compelling literature documents that there is much that is physical in mental disorders and much that is mental in physical disorders. The problematic terminological divide between mental and physical is also enshrined in the provision of a separate axis in *DSM-III-R* for physical disorders (axis III) and a separate section for organic mental disorders. The problem raised by the term "mental disorders" is clearer than its solution. The term "psychiatric disorders" would replace "mental disorders" with a descriptive and nonreductionistic construct but has its own connotation problems, particularly insofar as it might be construed to reflect professional boundaries.

Is DSM *Atheoretical?*

The introduction to *DSM-III* states that the system attempts to be atheoretical in regard to etiology and usable across the varying orientations that inform psychiatry. This assertion has been repeatedly criticized and misunderstood. It would be expecting too much to think that any frame of reference can be totally without theoretical assumptions (51). Preference for a descriptive approach that minimizes clinical inference is itself a theoretical position, and one that possibly is more useful within the biological and behavioral orientations. It is no surprise that psychodynamic and family clinicians have felt particularly dissatisfied with the *DSM* system (5–8, 52–56). Active review is underway to determine the available data and/or the need for additional research relevant to the development of psychodynamic and family contributions to classification. Nonetheless, it must be recognized that these fields have only recently developed a systematic interest in diagnosis, and much additional work is necessary before the classification can adequately reflect their perspectives. Suggestions not yet ready for inclusion in the body of the system might appear in a *DSM-IV* appendix or the *Source Book* to stimulate the additional necessary research.

Multiple Diagnosis, Comorbidity, and Differential Diagnosis

A number of features built into *DSM-III* resulted in most patients meeting criteria for more than one disorder. *DSM-III-R* went even further in encouraging multiple diagnoses by removing many of the diagnostic hierarchies and exclusion criteria that were included in *DSM-III* (14). The profusion of new categories and the division of old ones in *DSM-III* and *DSM-III-R* have also increased multiple diagnoses. *DSM-I* had 106 different categories, *DSM-II* had 182, *DSM-III* listed 265, and *DSM-III-R* included 292. The more diagnoses included in a system, the more clearly these are defined, and the fewer the exclusionary hierarchies, the more multiple diagnoses there will be.

The trend toward multiple diagnosis is neither good nor bad so long as its implications are understood (14, 57–61). The extensive recent literature on comorbidity of psychiatric diagnoses often assumes naively that a patient meeting criteria for more than one diagnosis has multiple independent conditions. This is certainly not the only possible relationship (60). Some separately labeled co-occcurring disorders may just as plausibly be considered part of a single complex syndrome that has been split apart in the *DSM* definition. In other cases, multiple diagnosis may result from definitional artifacts caused by similar items that overlap across different disorders.

DSM-III-R shifted the emphasis of the diagnostic process toward multiple diagnosis and away from differential diagnosis by removing many of the diagnostic exclusion criteria that established a hierarchical ranking of "more" versus "less" fundamental disorders (14, 60, 61). This approach saves information, improves reliability, and is in the atheoretical spirit of avoiding assumptions about priority that are difficult to make in clinical practice and unsupported by empirical evidence. Certain important differential diagnoses remain in *DSM* and are highlighted whenever exclusionary criteria are present. Future advances in knowledge beyond the descriptive validity of diagnoses will increase the precision and importance of differential diagnosis.

Categories, Dimensions, and Prototypes

The introduction to *DSM-III-R* states that "there is no assumption that each mental disorder is a discrete entity with sharp boundaries (discontinuity) between it and . . . no mental disorder" (p. xxii). Nevertheless, *DSM-III-R* follows the tradition of providing categorical diagnoses, which are most useful for labeling conditions with sharp boundaries. In using the categorical model, one must recognize its limitations (45). Kraepelin, best known for his emphasis on demarcating distinct syndromes (2, 24), acknowledged that "wherever we try to mark out the frontier between mental health and disease, we find a neutral territory, in which the imperceptible change from the realm of normal mental life to that of obvious derangement takes place" (62, p. 295). There is an accumulation of recent reports in the literature that suggest ways of modifying the assumptions of the categorical approach in order to make it more useful in psychiatric diagnosis.

A classical categorical approach would assume that all members of a class are homogeneous and that different classes are mutually exclusive. These standards are difficult to meet and fail to do justice to the complexity of psychiatric disorders. In contrast, a prototypic categorization sorts patients on the basis of the degree to which they resemble the prototype of the category (63–66). There are no features that completely define the category, and it is expected that different class members will differ in how closely they resemble the prototype and one another. A prototypic approach accepts that members of a class are likely to be heterogeneous even in their defining features and that border cases will be difficult to sort in any but a probabilistic fashion. This attitude is more congruent with polythetic than with monothetic sets of criteria, since the former, by definition, accept class heterogeneity. A prototypic view of diagnosis depends more on pattern recognition and family resemblance than on pathognomonic decision-tree logic.

The implications of a more prototypic attitude toward *DSM-IV* would be less apparent in its format than in the way it is used. If one regards the *DSM-IV* categories as prototypes, one is less likely to reify categories and more likely to respect boundary cases rather than trying to force them into one or another category (63). A research consequence of a prototypic approach is the realization that different patients approximate the prototype with different degrees of fidelity which should be assessed and studied (64). Some research projects should probably use more restrictive criteria to focus on prototypic patients. In other designs, it is important to have a wider range of pathology to increase generalizability. Although accumulating research results support the dimensional model of classification, particularly for personality disorders (65, 66), there are insufficient data at this time to justify a radical change in the format for clinical diagnosis.

CONSTRUCTION OF SETS OF CRITERIA

Clinical Versus Research Criteria

In contrast to *DSM-III-R*, which provides just one set of diagnostic criteria to be used for both clinical and research purposes, *ICD-10* has separate clinical and research criteria (67). The *ICD-10* approach has the advantage that each form of the classification meets the needs of its intended audience (i.e., more descriptive for the clinician, more specific for the researcher) but the disadvantage that it reduces the generalizability of research findings to clinical practice. *DSM-IV* will continue to have one set of criteria for use in both clinical and research practice in order to facilitate the necessary dialogue and mutual influence between them.

Core Versus Discriminating Features

The *DSM-III-R* criteria are used for two related but also separable activities: to define mental disorders and to diagnose them (68, 69). To serve both purposes, the ideal criterion would both capture the core of the definition of the disorder and maximize its distinction from near neighbors. Often enough, both functions are well served by the same item (e.g., thought disorder is both a core component of schizophrenia and useful in distinguishing it from paranoid and affective disorders). Unfortunately, items at the core of the definition are sometimes poor at discriminating the disorder, and items that are more discriminating may not be close to the core. Hallucinations in schizophrenia and impulsivity in borderline personality disorder are core aspects that are not discriminating because they are also frequent in disorders that are near neighbors.

Given the lack of pathognomonic items to identify most psychiatric disorders, how do we balance attention to core features and discriminating features? This is generally done by balancing sensitivity (which reflects the degree to which the item is typical of the disorder) with specificity (which reflects its discriminating value) (70, 71). One must recognize, however, the great impact on specificity that is exerted by the selection of comparison groups in a given study. For example, impulsivity is much more specific to borderline personality disorder in an outpatient clinic than in a prison or drug treatment setting.

Level of Clinical Inference in Criteria

The explicitness of the *DSM* diagnostic criteria has been the major source of improved reliability. Nonetheless, increased reliability may not always result in improved validity (72) or clinical utility (7). For example, the *DSM-III* criteria for antisocial personality disorder may compromise validity by emphasizing easily identifiable delinquent behavior (73–75) at the expense of more inferential aspects of the syndrome (e.g., lack of guilt and failure to bond). Reducing the level of clinical inference raises reliability but narrows the construct and reduces the role of clinical judgment. Moreover, as diagnostic items become more specific, more items are needed to represent the construct adequately. This results in cumbersome sets of criteria that reduce clinical utility.

Polythetic Versus Monothetic Criteria

There was an increased use in *DSM-III-R* of polythetic sets of criteria which do not require that all items be present for the diagnosis to be made (3). Monothetic sets imply that diagnostic features are more pathognomonic than is usually the case, exclude items that are useful but are not always present, and are usually less reliable because the limiting factor in the reliability of the entire diagnosis becomes the reliability of its least reliable item (65). However, there are also disadvantages in the use of polythetic sets of criteria. They tend to become complex and may allow for more heterogeneity in the diagnosis than is desirable. For example, there are 93 different ways to meet the criteria for borderline personality disorder (76), and two patients may each meet the criteria for schizotypal personality without sharing even a single criterion for the diagnosis.

Diagnostic Test Results as Criteria

Diagnoses in the rest of medicine are often heavily influenced by laboratory tests. The increasing use of laboratory tests in psychiatry raises the question of whether results of these tests should be included in the sets of criteria. There are several possible relationships between test results and clinical observation. Test results may add sufficiently important information to clinical assessment (as in diabetes and pneumonia) that they serve as essential factors in making the diagnosis. The only areas in psychiatry in which this may now be true are some of the organic disorders, mental retardation, learning disabilities, and, arguably, some specific sleep disorders.

At a lower level of predictive value, test results may not be essential for diagnosis but may have sufficient sensitivity and specificity to enhance clinical data and deserve inclusion in sets of polythetic criteria. It is controversial which, if any, of the tests currently used in psychiatry (e.g., sleep architecture, neuroendocrine challenge, imaging, and psychological tests) have demonstrated sufficient ability to discriminate patients with particular disorders from the wide variety of comparison groups that require differential diagnosis. In fairness, it should also be noted that proponents of a test argue that its performance is limited by the reliability of the clinical diagnosis, so that failures of concordance between test results and clinical diagnosis may point to the weakness of the latter rather than the former.

At yet a lower level of specificity, a test result may correlate with a diagnosis without being sufficiently specific and predictive to diagnose a given patient (e.g., imaging findings in schizophrenia). Such test results might be discussed in a text section of *DSM-IV* and inform the choice of criteria but could not serve as a criterion.

WORK GROUP ISSUES

Having reviewed the general concepts and principles underlying the deliberations of the Task Force on *DSM-IV*, we turn now to a survey of the specific diagnostic issues under review by a number of the task force's work groups. These will not only illuminate the practical problems involved in devising diagnostic classifications but will also, we hope, stimulate our colleagues to offer their own suggestions and solutions.

Anxiety disorders. The threshold for the *DSM-III-R* diagnosis of panic disorder, which requires at least four panic attacks in a 4-week period, was established without empirical support and is being reconsidered because of concern that it may be too restrictive. There are proposals to split social phobia into generalized and circumscribed subtypes and to split simple phobia (to be renamed "specific phobias") into specific subtypes (e.g., blood-injury, situational, animal) in order to provide greater specificity. The difficult boundaries dividing panic disorder, social phobia, and specific phobias are being studied. There are proposals for adding subtypes to obsessive-compulsive disorder to indicate the degree of insight, to increase the emphasis on cognitive compulsions, and to clarify the definitional boundaries with delusional, somatoform, and phobic disorders (and normality). The work group is studying the degree of stressor severity that should be required for posttraumatic stress disorder and whether this should include subjective reactions. Finally, the group is considering the utility of a category for mixed anxiety/depression, reported to be encountered frequently in primary care and outpatient settings.

Child and adolescent disorders. This work group is examining whether the adult criteria for mood, anxiety, and psychotic disorders adequately describe children suffering from these disorders. Attempts are being made to reformulate into unified categories several disorders that have been split along age boundaries (e.g., avoidant disorder of childhood and social phobia; gender identity disorder of childhood, gender identity disorder of adolescence or adulthood, nontranssexual types, and transsexualism). The group is also studying the implications of the much broader definition of autistic disorder that was introduced into *DSM-III-R* and is comparing the *DSM-III*, *DSM-III-R*, and *ICD-10* definitions of autism by reanalyzing existing data, to be followed up by a focused field trial. Additionally, the group is reviewing the boundaries between conduct disorder and oppositional disorder and studying the association of hyperactivity with symptoms of attentional deficit.

Eating disorders. Reflecting evidence that individuals who keep their weight low and also binge are best conceptualized as having only one eating disorder (i.e., anorexia nervosa), the group is considering excluding the additional diagnosis of bulimia nervosa and instead subtyping anorexia nervosa to indicate the presence of binges. It is also reviewing evidence for a new category, pathological overeating syndrome.

Late luteal phase dysphoric disorder. The suggestion that this disorder be included in *DSM-III-R* generated substantial controversy, and instead it was included in an appendix. In order to ensure a thorough and objective review of evidence in this area, we established a work group specifically to evaluate the prevalence, specificity, course, validity, and implications of the proposed diagnosis and its relationship to other psychiatric and medical disorders. The crucial question is whether a syndrome occurs that is impairing, is limited to a relatively small percentage of women, is subject to reliable diagnosis, and has useful treatment implications. The syndrome must not occur exclusively in women who meet the criteria for other psychiatric diagnoses, with exacerbations in the late luteal phase. The optimal definition of the syndrome and the balance of emotional, behavioral, and physical symptoms are also being reviewed.

Mood disorders. This work group has reviewed the literature on the validity of the concept of melancholia as a qualitatively distinct form of depression, the relationship of chronic major depression and dysthymia, and the support for potential subtypes, such as atypical depression, postpartum depression, rapid-cycling bipolar disorder, and bipolar II disorder. Modifiers describing course of illness for depressive disorders are being developed, and their feasibility in clinical settings is being studied. The criteria for seasonal affective disorder are being reexamined because of concerns that the current criteria are too rigid.

Multiaxial system. The multiaxial system, one of the major innovations in *DSM-III*, was included to provide a more complete description of the patient, but the problem is whether the current axes are optimal. Specifically, there is concern about the relative underutilization of axes IV and V and ways to improve them. Axis IV might be reconceptualized either to code external problems (and/or assets) that may have an impact on the disorders coded on axes I, II, and III or to provide a rating of social support. The work group is also considering a reformulation of axis V in which psychiatric symptoms would not be aggregated with issues of general functioning. There are also suggestions for possible additional axes for rating defense mechanisms and/or family functioning. It is not clear whether *DSM-IV* will retain the current five-axis system, add additional axes, or have a three-axis system. One suggestion has been to retain the three diagnostic axes for general purposes and provide an array of optional specialized (and basically nondiagnostic) axes that could be applied in the settings to which they are most pertinent.

Organic disorders. This work group is considering a proposal by Spitzer et al. (77) that would eliminate the term "organic" and reformulate the Organic Disorders section. Dementia, delirium, and amnestic disorder would remain together in a section that might be named "Cognitive Impairment Disorders," but the other currently listed "organic disorders" (e.g., mood, anxiety, personality) would be renamed "secondary" or "drug-induced" and listed within the pertinent section containing their descriptive phenomenology.

Personality disorders. The most compelling issue concerns the attempt to become more consistent in assigning categories for disorders that may have a spectrum relationship to axis I conditions and have an early and insidious onset, a stable course, and a pervasive manifestation. *DSM-III-R* inconsistently places dysthymia and cyclothymia with axis I mood disorders but includes schizotypal disorder with personality disorders. *ICD-10* places schizotypal disorder within the schizophrenia section, and this has been proposed for *DSM-IV*. The problem with this solution is that several other disorders currently classified as personality disorders may have a similar spectrum relationship to axis I disorders (e.g., avoidant personality to social phobia). This work group is also involved in a study comparing various ways of defining antisocial personality disorder in an effort to determine whether the criteria can be simplified and/or modified to include some of the traditional personality attributes of psychopathy. The very limited literature on self-defeating and sadistic personality disorders, which were placed in an appendix in *DSM-III-R*, is also being reviewed.

Psychiatric system interface disorders. This work group is charged with studying a number of disorders that often present at the interface between psychiatry and other medical disciplines. It is reviewing a method to simplify the now very complex criteria for somatization disorder. It is considering a new category, acute stress reaction, currently in *ICD-10*, to describe cases in which there is an acute and severe reaction to stress consisting of dissociative and/or anxiety symptoms. There is also a proposal to bring greater specificity to the category of psychological factors affecting physical condition by adding subtypes to indicate the nature of the psychological factors. Intermittent explosive disorder is being reviewed for possible elimination because of concern that there may be no cases of explosive behavior that cannot be accounted for by another axis I, II, or III condition. Finally, this work group is also considering how *DSM-IV* can best be applied to primary care settings.

Psychotic disorders. DSM-III markedly narrowed the construct and prevalence of schizophrenia, particularly by providing a broadly inclusive category for mood-incongruent psychotic mood disorders. *DSM-III-R* narrowed the definition of schizophrenia even further by broadening the criteria for the delusional disorders. The work group is considering whether the *DSM-III-R* construct is too narrow, whether negative symptoms should be given greater prominence as defining features, the value of including prodromal and residual phases in the definition of schizophrenia, and the optimal method of subtyping (particularly, whether it is possible to make clear that catatonia often occurs in association with other disorders). The group is reviewing ways of reconciling the very different *DSM* and *ICD* constructs for schizophrenia, with special focus on the different duration requirements. It is also examining the advisability of adding the construct of simple schizophrenia (i.e., presence of negative symptoms of schizophrenia without positive symptoms, but with deterioration).

Sexual disorders. The work group has focused on refining the diagnostic criteria to increase their clinical utility for the general clinician. The boundary between transvestic fetishism and gender identity disorder is being studied to determine how best to classify individuals with features of both.

Sleep disorders. One of the most controversial issues in *DSM-III-R* was whether the results of sleep laboratory tests should be included in the diagnostic criteria. The work group is considering ways to integrate clinical and laboratory data in a modular fashion that allows for different degrees of certainty in making the diagnoses. The group is working toward a diagnostic system that is compatible with but less specific than the *International Classification of Sleep Disorders* to ensure that any proposals for *DSM-IV* will be compatible.

Substance use disorders. This group is exploring the impact of the broadened definition of substance dependence—with its increased emphasis on compulsive use and lack of a requirement for tolerance and withdrawal—that was incorporated into *DSM-III-R*. It is studying the implications of providing a more specific and inclusive definition of abuse, which was made a residual category in *DSM-III-R*. The group is also reviewing data on the best definition of full and partial remission, on the protracted abstinence syndrome, on nicotine abuse, and on the value of a familial/nonfamilial distinction for subtyping alcoholism. It is studying various ways of defining when psychopathology is best considered secondary to substance intoxication or withdrawal.

This concludes our brief summary of the major questions facing the *DSM-IV* work groups. Interested readers are invited to consider the options being studied by the work groups and to provide us with suggestions, criticisms, and, perhaps most welcome of all, additional data to help inform our decisions.

CONCLUSIONS

Perhaps the major theme that emerges from this overview is that no diagnostic system can ever completely satisfy everyone or every need. The task of developing *DSM-IV* involves decisions that balance competing plausible alternatives. The major methodological innovation of *DSM-IV* will be its effort to move beyond expert consensus by placing greater emphasis on the careful, objective accumulation of empirical evidence. The spirit of *DSM-IV* will be conservative. Suggested revisions will have proved their worth after rigorous literature reviews, data reanalyses, field trials, and inspection by members of the mental health professions. Two other goals guiding changes in *DSM-IV* are a desire to increase the compatibility between the *DSM* and *ICD* systems and an effort to make *DSM-IV* simpler, clearer, and more clinically useful. The threshold for including new diagnoses in *DSM-IV* is also much higher than it was in *DSM-III* and *DSM-III-R*.

In this article we have discussed a number of the conceptual problems that underlie the development of the diagnostic system in the hope that this will improve the way in which *DSM-IV* will be understood and used. This midterm progress report on our work is meant to stimulate discussion both on the general issues in psychiatric classification and on the specific suggestions that have been made for *DSM-IV*.

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A Critical Review of Epidemiological Studies of Puerto Rican Mental Health

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Through a review of the epidemiological literature on the mental health of Puerto Ricans and other Hispanics, the authors argue that lack of attention to cultural issues in epidemiological studies leaves many questions unanswered and raises concerns about the validity of studies in this area. The authors point out that the mental health status of Puerto Ricans in New York City is still poorly understood after 30 years of research. The roles of cultural response styles and of culturally meaningful expressions of distress in shaping responses to research interviews should be central concerns in developing research in cross-cultural psychiatry.

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Through a review of the epidemiological literature on the mental health of Puerto Ricans and other Hispanics, we will argue that lack of attention to cultural issues in epidemiological studies leaves many questions unanswered and raises concerns about the validity of studies in this area. The mental health status of Puerto Ricans in New York City is still poorly understood after 30 years of research. This critical review is not a comprehensive study of the literature on Puerto Rican mental health. It is a review of the epidemiological studies of Puerto Rican mental health on the mainland United States and in Puerto Rico, from the perspective of a growing literature in medical anthropology on cultural dimensions of illness experience and behavior. In particular, we argue that a number of problems identified in more than three decades of epidemiological studies can be partially understood by viewing these findings in the context of two popular illness categories, *nervios* and *ataques de nervios,* which are common expressions of distress among Puerto Ricans. These problems include 1) the high prevalence of psychiatric symptoms reported by Puerto Ricans during psychiatric interviews, 2) the social desirability of symptoms and an acquiescent response style as explanations for the high rates of reported symptoms, and 3) the role of somatization as a culturally meaningful expression of psychological distress. On the basis of medical anthropology and cross-cultural psychiatry we will develop an approach to the question of whether a high level of symptoms reflects a high prevalence of psychiatric disorder or problems with the norms and validity of psychiatric research interviews. The roles of cultural response styles and of culturally meaningful expressions of distress in shaping responses to research interviews are central to developing research in cross-cultural psychiatry.

OVERVIEW OF *NERVIOS* AND *ATAQUES DE NERVIOS*

Before beginning our review, we will briefly define *nervios* and *ataques de nervios* and direct readers to appropriate clinical and anthropological literature for exploration of these concepts in more detail (1–16). *Nervios* ("nerves") and *ataques de nervios* ("attacks of nerves") have been discussed in the psychiatric and anthropological literatures for over 30 years.

Nervios refers to a chronic and more generalized sense of distress and upset experienced by Puerto Ricans and other Latinos as a result of a variety of life stresses (3, 6, 9–11). The symptoms of *nervios* include a range of psychosomatic experiences, most prominently headaches, heart palpitations, a sense of heat in the chest, generalized bodily pains, trouble sleeping, and persistent worrying. The social sources of *nervios* are a variety of personal, familial, and social problems that result from losses of key personal relationships. In contrast, an *ataque de nervios* is a more defined and dramatic episode. *Ataque de nervios* is a culturally sanctioned response to an acute stressful experience,

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particularly relating to grief, fear, or family conflict (1, 4, 5, 7, 8). *Ataques de nervios* are characterized by a number of symptoms, including trembling, heart palpitations, a sense of heat in the chest rising into the head, faintness, and seizure-like episodes. A typical attack occurs at a culturally appropriate time, such as during a funeral, at the scene of an accident, or during a family argument or fight. Such an attack calls forth the support of the person's social network. The person usually regains consciousness rapidly and does not remember the *ataque de nervios*. Actual episodes brought to the attention of medical personnel and/or folk healers are much more varied and can involve experiences that deviate in a variety of ways from this cultural norm.

The early psychiatric articles on the subject focused on early childhood socialization and intrapsychic factors as the major triggers of an *ataque de nervios* (4, 12, 14–16). More recent articles by anthropologists and mental health investigators have reconceptualized such attacks through an understanding of their cultural meaning and the broader social factors that provoke them (1, 2, 5, 7, 8, 13).

HISTORICAL REVIEW OF STUDIES OF PUERTO RICAN MENTAL HEALTH

The most striking feature of the literature on Puerto Rican mental health on the U.S. mainland is that in spite of several decades of research (17–27), data on the actual prevalence of psychiatric disorder among Puerto Ricans on the mainland United States are still inconclusive. From the earliest studies of inpatient samples (17) to more recent surveys using standardized symptom checklists and diagnostic interviews (24–26), Puerto Ricans in mainland U.S. cities have appeared to experience more distress than other ethnic groups or Puerto Ricans on the island of Puerto Rico. The symptom ratings of mainland Puerto Ricans on various scales—from the 22-item scale of the Midtown Manhattan Study (18) to the Center for Epidemiologic Studies Depression Scale, used in the Hispanic Health and Nutrition Examination Survey (24)—have been consistently higher than those of whites or other minority groups, both Hispanic and non-Hispanic. A second consistent finding, which makes the high rates of symptoms difficult to interpret, is that Puerto Ricans are more apt to respond positively to items on a symptom checklist because the symptoms are viewed as less socially undesirable and because Puerto Ricans are more willing to report symptoms than other ethnic groups; this willingness is often referred to as a more "acquiescent response style" (19–23).

The central questions in the first section of our review are, Why do Puerto Ricans report more symptoms than other groups? and, Is the higher rate of symptoms a result of greater pathology or of response style?

Early Studies of Hospitalization Rates

To our knowledge, Malzberg (17) was the first writer to raise the issue of higher rates of mental disease among Puerto Ricans in New York City. He identified Puerto Ricans as the third major wave of migration to New York City; southern blacks, coming in the 1920s and 1930s, were the first, and refugees from Europe, who came in the 1930s and 1940s, were the second. While Puerto Ricans had been coming to New York since the 1920s, the great surge in Puerto Rican migration began in the 1940s and continued through the 1950s. Malzberg identified poverty and language barriers as the major problems facing Puerto Ricans in New York. He noted that the average rate of first admissions to psychiatric hospitals for Puerto Ricans in New York was higher than the rate in Puerto Rico (although he also noted that hospital services in Puerto Rico were quite limited). He also observed that those admitted were poorer and more dependent on public facilities than patients from other ethnic groups. He pointed out that equal numbers of men and women were being admitted, whereas in the total population women had a higher rate of psychiatric treatment. When the rates were standardized to the age and sex distribution of the population, Puerto Rican men had a significantly higher rate of admission than Puerto Rican women. Over half of the Puerto Ricans were admitted for dementia praecox, whereas only about 30% of non-Puerto Ricans had this diagnosis. While Malzberg emphasized the role of social stressors—such as limited employment opportunities, language barriers, and residential concentration in areas with poor housing—in producing mental illness, he also raised the possibility that the mentally ill were overrepresented in migratory populations and were not randomly selected from the home population. He concluded that Puerto Ricans had a significantly greater probability of developing a mental disorder than other New Yorkers and set the stage for the debate over social stress and social selection explanations of high rates of mental illness among migratory populations (27). These issues continue to be important in community studies of mental disorder in New York City and elsewhere.

Midtown Manhattan and Washington Heights Studies

The finding of high levels of pathology among the small number of Puerto Ricans (N=27) included in the total sample (N=1,600) of the Midtown Manhattan Study (18) has frequently been cited in the literature on Puerto Rican mental health. Not one of the Puerto Ricans was rated as well. In addition, 52% (12 of 23) of the Puerto Ricans reported that they experienced impairment in role function as a result of their symptoms, compared to 27% in the rest of the sample. These findings in a community study reinforced what Malzberg had found in his study of hospital admissions. However, the findings were so different for Puerto Ricans that they simultaneously raised questions about the sources of psychopathology and the validity of the findings themselves.

Dohrenwend and Dohrenwend's studies in the Washington Heights section of New York City led to a rethinking of these earlier findings, and their work continues to be one of the best statements of the issues in studying the mental health of minority populations who have recently migrated (19, 20). In his classic paper, "Social Status and Psychological Disorder," Bruce Dohrenwend (19) took on the social stress versus social selection hypotheses directly. He carried out a study in Washington Heights of 1,000 adults aged 21–59 years, with more balanced samples of Jewish, black, Irish, and Puerto Rican respondents than in the Midtown Manhattan Study. He used the same 22-item scale as in the Midtown Manhattan Study and used four or more symptoms as a cutoff point for determining impairment. Using both education and income (together and separately) as controls for cross-ethnic comparisons, he found that Puerto Ricans had a significantly higher rate of impairing symptoms than any of the other groups, including blacks. This raised questions about the social stress hypothesis, since blacks experienced similar levels of social deprivation.

Dohrenwend and Dohrenwend (20) went on to carry out a series of methodological investigations to better understand these findings. They looked at the following issues.

1. *Social desirability of the symptom items.* The researchers found a direct relationship between the level of symptoms reported and the perceived social desirability (or degree of undesirability) of the reported symptoms. They hypothesized that a high rate of symptoms among Puerto Ricans was "due to cultural differences in willingness to admit such symptoms when they are present, or to cultural differences in mode of expressing distress" (19, p. 25).

2. *Bias in symptom items.* The scale items were weighted toward anxiety and depression and did not tap sociopathic traits, alcoholism, or early symptoms of paranoid schizophrenia. When the researchers compared subsamples of ethnic groups on these latter traits, they found that blacks and Puerto Ricans scored higher in these areas regardless of socioeconomic levels, supporting the social stress hypothesis.

3. *Relation of psychological symptoms to psychological disorder.* The subjects with more symptoms had more intervening life events, raising the possibility that the symptoms were a result of stressful life events rather than of psychological disorder. Dohrenwend concluded that "while the results of field studies make it clear that there are group differences in modes of expressing distress, including some that are apparently stylistic, the studies are far from clear about the relations of these modes to underlying psychiatric conditions of individuals" (19, pp. 33–34).

Subsequent Studies of Puerto Rican Mental Health

Several authors building on these early efforts have emphasized the significant effects of response style on reports of symptoms. However, they have been unable to ascertain whether mainland Puerto Ricans actually have a higher rate of disorders than other ethnic groups, whether they report more symptoms, or both. Haberman (21) reanalyzed the data in the Washington Heights Study, comparing the data with those from the Public Image of Mental Health Services in New York City study. He found that there were important social and ethnic differences in the reporting of symptoms. Women, respondents with less education, and those with lower incomes were more likely to report four or more symptoms than men and respondents with higher socioeconomic status. Puerto Ricans had the highest percentage of reports of four or more symptoms in both the Washington Heights Study and the Public Image of Mental Health Services in New York City study. While close to 40% of Puerto Ricans reported four or more symptoms in both studies, less than 25% of the other ethnic groups surveyed reported four or more symptoms. In these studies, 90% of the Puerto Ricans had been born in Puerto Rico, whereas the other groups had much higher proportions of individuals born in New York City. Haberman concluded that Puerto Ricans were more likely to give affirmative answers because many of the questions were not seen as socially undesirable and because they were less likely to see deviant behaviors as signs of illness than the other ethnic groups. Haberman also argued for developing different cutoff scores for defining "caseness" when using symptom scales with multiethnic samples.

Haberman (22) did a follow-up study to see how reports of symptoms differed between Puerto Ricans in New York City and on the island of Puerto Rico. He focused on disentangling the relationship between reporting style and level of distress. "Thus, it seems that there are substantial differences between Puerto Ricans and other ethnic groups in modes of expressing distress, suggesting that rates of reported symptoms would be higher than their rates of disorder indicate" (22, p. 134). Haberman compared the responses to the 22-item scale used in the Washington Heights Study (1960–1961), the Public Image of Mental Health Services in New York City study (1963), and the Public Image of Mental Health Services in Puerto Rico study (1963–1964). Puerto Ricans in Puerto Rico indicated more symptoms than Puerto Ricans in New York. On the island, rural Puerto Ricans reported slightly more symptoms than urban Puerto Ricans. The number of reported symptoms declined with the length of time in New York City, suggesting an effect of acculturation on the reporting of symptoms and an effect of adjustments to New York and the building of new social networks. Haberman concluded that this pattern "makes culturally patterned differences in modes of expressing distress the most parsimonious explanation for the high rates of specific symptomatology mentioned" (22, p. 144).

Krause and Carr (23) carried out a multiethnic study in a Midwestern city in the mid-1970s. Their findings highlighted socioeconomic differences within ethnic groups as a key variable and addressed the role of the stresses of migration. Krause and Carr interviewed 219 persons from a variety of ethnic groups. They used only four of the 22 items from the scale used in previous studies, as they found that these four items correlated well with the whole scale and discriminated subjects with diagnosable psychiatric disorders from normal subjects, as did the full scale. The items used were "heart beating hard," "hands tremble," "acid or sour stomach," and "personal worries make me physically ill." Again, these researchers found the strongest relationship between acquiescent style of response to health items, assessed with an approach similar to that developed by Dohrenwend (19), and degree of symptoms. An acquiescent response style was much stronger among Puerto Ricans, who had the lowest level of education and most disadvantaged status of the ethnic groups studied. Within the Puerto Rican subsample (N=47), a higher number of reported symptoms was related to more recent migration, higher anomie score, lower education, older age, and female sex.

Discussion

The studies just reviewed consistently showed that Puerto Ricans reported more symptoms in response to the 22-item scale from the Midtown Manhattan Study than other ethnic groups. The researchers all concluded that response style was the best explanation for these differences and that culture was the major factor affecting response style. Yet despite intense investigation, none of the studies explored the nature of the culturally patterned differences that would account for this uniquely Puerto Rican response style. Aside from the stress and selection theories of distress among Puerto Ricans, this literature has provided relatively little speculation on what dimensions of Puerto Rican culture produced the behavior labeled as "expressive" or "acquiescent" and led Puerto Ricans to view symptoms as less socially undesirable. Research from medical anthropology suggests an alternative perspective to the social stress and "Puerto Rican personality style" explanations for these differences in illness behavior. Medical anthropologists argue that culture provides ethnotheories of illness—systems of defining, categorizing, and evaluating symptoms and popular forms of illness; typical modes of communicating distress; and distinctive syndromes of symptoms locally recognized and labeled.

Medical anthropology research among Puerto Ricans points to some dimensions of popular medical culture that help to explain these findings. One hypothesis is that the symptoms covered by the 22-item scale fit closely the characteristics of *nervios* and that what made Puerto Ricans respond so readily to the scale is that the instrument was tapping a culturally salient syndrome for them. *Nervios* is a culturally meaningful idiom of distress among Puerto Ricans (and other Latinos) that would be expected among a group of recently arrived immigrants to New York City, especially since these families were socially isolated, economically disadvantaged, and discriminated against (6, 9, 10). Women are more likely to suffer from *nervios,* as are people from rural areas and those with lower socioeconomic status. Thus, the reason that Puerto Ricans found the symptoms on the 22-item scale socially acceptable and culturally meaningful was that they fit the category of *nervios,* which expressed the worries, troubles, and problems of Puerto Ricans recently arrived in a major urban center on the mainland.

We contend that this example highlights a broader problem in the study of Puerto Rican mental health and, more generally, in research in cross-cultural psychiatry. Culture structures how people respond to symptom questions and how they organize symptoms into syndromes. Later in this review we will highlight a similar problem in the relationship between panic disorder and the cultural syndrome of ***ataques de nervios*** as another example of the confounding of psychiatric diagnosis and local conceptions of disorder.

RECENT STUDIES OF PUERTO RICAN MENTAL HEALTH

In the context of this historical overview, we will review two major studies of the mental health of Puerto Ricans that used newer psychiatric interviews: the Center for Epidemiologic Studies Depression (CES-D) Scale and the NIMH Diagnostic Interview Schedule (DIS). Both of these interviews have better reliability than earlier symptom questionnaires. They also suffer less from confounding physical and psychological symptoms. However, the validity of these interviews for cross-cultural research is still a central concern, as highlighted by recent studies of Puerto Rican mental health.

The CES-D Scale was developed by researchers at NIMH (28) to be used in community studies to identify people with significant depressed affect. It is a symptom checklist that asks about symptoms during the previous 2 weeks. In contrast to earlier symptom checklists, such as the 22-item scale used in the Midtown Manhattan Study and other studies, it is more weighted toward the affective symptoms of depression.

The DIS is a structured psychiatric interview (29) developed for use in the Epidemiologic Catchment Area (ECA) program funded by NIMH to assess the mental health of the U.S. population (30). Unlike earlier psychiatric interviews, it provides *DSM-III* diagnoses based on the reports of symptoms and behaviors.

Both the CES-D Scale and the depression section of the DIS were used in the Hispanic Health and Nutrition Examination Survey, a major national study developed to assess health conditions and health needs of the Hispanic population in the United States. It was carried out in 1984. The sample included Puerto Ricans in the New York metropolitan area, Cuban-Americans in Miami, and Mexican-Americans in the Southwest. The Puerto Rico Island Study, also carried out in 1984, surveyed the mental health of Puerto Ricans in Puerto Rico with a translation of the DIS; the subjects were a random sample of the entire Puerto Rico population. In the following sections we review studies that have explored the role of culture in shaping responses to these standard psychiatric interviews.

Hispanic Health and Nutrition Examination Survey

The Hispanic Health and Nutrition Examination Survey indicated much higher rates of both symptoms of depression and depression "cases," according to the CES-D Scale, and a higher prevalence of major depressive episode, according to the DIS, among Puerto Ricans in New York than among Cuban-Americans or Mexican-Americans (24). Twice as many Puerto Ricans as Mexican-Americans met the CES-D Scale criteria for "caseness" and had experienced a major depressive episode. Compared to Cuban-Americans, almost three times as many Puerto Ricans met the CES-D caseness criteria, and more than twice as many met the criteria for major depression.

The higher CES-D Scale scores need to be interpreted with some caution. Recent analyses by Angel and Guarnaccia of the Hispanic Health and Nutrition Examination Survey data indicate consistent differences in the way Hispanics conceptualized depression, as reflected in the factor structures of the CES-D Scale (25) and a conflation of physical health status with psychological state (26). In an analysis of the factor structure of the CES-D Scale, the overall structures of the factors were quite similar for Mexican-Americans, Cuban-Americans, and Puerto Ricans (25). Each group's scores yielded a three-factor solution in which a combined affective and somatic factor accounted for the greatest explained variance. This factor structure was different from that found by Radloff (28) for Anglo-Americans and by Roberts (31) for a multiethnic sample including Mexican-Americans. In both studies, the researchers identified separate factors for depressed affect and somatic/retarded activity. The combined affective and somatic factor identified by Guarnaccia et al. (25) fits more closely with other research which has found that Hispanics' expressions of distress focus on somatic idioms.

The results of this analysis of the factor structure of the CES-D Scale for Hispanics raise questions about validity in the cross-cultural measurement of symptoms of depression. If the pattern and meaning of symptoms differ significantly between non-Hispanics and Hispanics, their symptom reports must be interpreted differently. Caution is needed in using caseness criteria, as the report of a large number of symptoms may not be a good indication of clinical depression for Hispanics. Equally defensible is the argument that Hispanics report symptoms of demoralization because of their disadvantaged social status or that reports of large numbers of symptoms on scales such as the CES-D Scale reflect the culturally meaningful syndrome of *nervios*. The higher rates of symptom reports among Puerto Ricans in New York can be best accounted for by the fact that they are more socially disadvantaged than the other Hispanic groups.

In a related study, Angel and Guarnaccia (26) compared reports of depressed affect and of physical health problems in the Hispanic Health and Nutrition Examination Survey. For all Hispanic groups, the subjects who reported the worst health had the highest average CES-D Scale score. The largest difference revealed by this study was the consistently higher CES-D scores for Puerto Ricans at all levels of self-reported health. Puerto Ricans who rated their health as poor had an average CES-D score well above 16, which is often used as a cutoff for depression. Low levels of both education and income were associated with poorer self-assessments of health status. This study made clear that health, cultural factors, and social class affect an individual's self-assessment of his or her health simultaneously. These findings raise further questions about the source of high rates of depressive symptoms among Puerto Ricans and the role of somatization in Puerto Ricans' response to symptom checklists. The comparison among Hispanic groups further supports the social stress hypothesis, as Puerto Ricans exhibit higher rates of unemployment, low income, and marital disruption than either Mexican-Americans or Cuban-Americans.

Puerto Rico Island Study

The striking finding of the Puerto Rico Island Study is that there was no major difference between the rates of mental disorder in Puerto Rico and the five sites of the ECA study on the mainland United States (32). Using a standardized diagnostic interview, investigators found that the prevalence of mental disorder was no higher among Puerto Ricans in Puerto Rico than among people from a variety of ethnic and social class backgrounds on the mainland United States. These findings contradict those from earlier studies, particularly that by Haberman (22), which suggests more reports of distress in Puerto Rico. Canino et al. (32) offered the following explanation for the high rates of reported distress among Puerto Ricans in the earlier study: "Previous reports of higher rates of disorder in Puerto Rican populations are not confirmed by our results and are probably related to the methodology through which disorder was measured. Instruments used in those studies were not linked to specific diagnostic categories or criteria. Perhaps Puerto Ricans report more symptoms than other ethnic groups and therefore score high on dimensional measures of psychopathology." However, differences between Puerto Ricans and other Hispanics in the Hispanic Health and Nutrition Examination Survey indicate a higher prevalence of disorder among Puerto Ricans living in the New York metropolitan area, according to the DIS depression schedule. The lifetime rate of major depressive episode for mainland Puerto Ricans in the Hispanic Health and Nutrition Examination Survey was 8.9% (24), as compared to 4.6% in the Puerto Rico Island Study (32), 4.6% for Mexican-Americans in the Los Angeles segment of the ECA program (33), and 4.2% for Mexican-Americans in the Hispanic Health and Nutrition Examination Survey (24). These findings raise important questions about past studies that compared Hispanics in their home countries and the United States but did not include careful analysis of migration patterns, and they pose significant challenges to future studies of Hispanic mental health. While it continues to appear that the rates of both distress and disorder are higher for Puerto Ricans in New York, the explanation and validation of these differences remain elusive.

Ataques de Nervios *in the Puerto Rico Island Study*

Guarnaccia et al. (34) examined the effect of *ataques de nervios* on responses to a Spanish version (35) of the DIS in Puerto Rico. One of the few striking differences between the Puerto Rico study (32) and the ECA program on the mainland United States was a higher rate of somatization disorder and a higher mean number of total symptoms reported in the somatization section of the DIS. In analyzing the factor structure of the major diagnostic categories of the DIS, Rubio-Stipec et al. (36) discovered that when similar analyses were done with the Los Angeles and St. Louis data from the ECA program, there was a somatization factor which was unique to the Puerto Rico study. Upon reviewing the factor for somatization, Guarnaccia et al. (34) identified a cluster of symptoms that corresponded to an *ataque de nervios*.

Guarnaccia et al. (34) created a scale to measure the Puerto Rican cultural idiom of distress *ataques de nervios,* using 12 of the relevant symptom items from the somatization section of the DIS. Of the 1,513 people in the sample, 348 (23%) fit the *ataque de nervios* category according to the symptom scale created. Women were significantly overrepresented in the *ataque de nervios* group, as were people over the age of 45. People in this group also were of significantly lower socioeconomic status according to several indicators. More of them had experienced a divorce or separation or were widowed. These social characteristics of sufferers of *ataques de nervios* fit closely the descriptions of *ataque* sufferers found in both anthropological and clinical studies. They also closely match the social characteristics of subjects reporting more symptoms in the earlier studies reviewed.

While *ataques de nervios* are traditionally thought of as normal expressions of distress among Puerto Ricans and are not associated with psychopathology, a significant proportion of the people in the *ataque de nervios* group met the DIS/*DSM-III* criteria for a number of psychiatric diagnoses. Particularly high rates of major depressive episode, dysthymia, agoraphobia, and phobic disorder were found in this group. Subjects who reported symptoms of *ataques de nervios* were also more likely to seek help both in the professional and folk medical sectors in Puerto Rico. Guarnaccia et al. also developed case narratives of *ataques de nervios* using descriptions of panic episodes collected by the interviewers with the panic section of the DIS. Several of these case descriptions indicated that people who responded positively to the panic screening question identified their experience as an *ataque de nervios* and described experiences commonly associated with such attacks: death of a loved one, conflict with a partner, and loss of family support, often related to migration.

CONCLUSIONS

Cross-cultural psychiatric studies would be considerably strengthened if they addressed culturally important categories of mental distress with instruments constructed to measure local categories at the same time that they determine *DSM-III* psychiatric diagnoses (37–43). Development of instruments that include culturally meaningful illness categories requires the same kind of detailed knowledge of these disorders that psychiatrists have of *DSM-III* diagnoses. Most psychiatric epidemiologists do not currently possess this knowledge. Teams studying cross-cultural psychiatry need to include researchers who are attuned to, and know how to ethnographically interpret, the local knowledge of the people being studied.

This overview of studies raises significant questions about the cross-cultural validity of several diagnostic categories, especially as they are operationalized in the DIS. The panic disorder section of the interview is one of those found to be problematic. Many of the DIS panic symptoms reflect *ataques de nervios,* and several of the descriptions of these episodes identified them as this cultural expression of distress (34). In this sense, *ataques de nervios* could be considered a cultural idiom that comprises a cluster of symptoms similar to a panic attack. This does not imply a one-to-one correspondence in Puerto Rico between panic attacks and *ataques de nervios*. The panic questions provided a limited entree for Puerto Ricans to talk about their *ataques de nervios*. However, the research data would be greatly improved and amplified by adding a section on *ataques de nervios* and rewording the panic question to remove ambiguity from it.

This review also raises serious questions concerning the cross-cultural validity of the diagnosis of somatization disorder. Many studies have shown that Latinos report more somatic symptoms than other cultural groups (26, 44–48). A higher prevalence of somatization disorder was found in Puerto Rico (32). However, when one looks at the patterns of responses to the somatization section of the DIS with an understanding of the local culture, it becomes clear that reporting somatic symptoms is an illness behavior shaped by local categories of distress, by the health care systems people are socialized in, and by the stigma of mental illness.

The striking result of this review is that serious questions about the mental health status of Puerto Ricans still remain after 30 years of research in this area. The most recent studies strongly indicate that Puerto Ricans in New York report more psychological distress than Puerto Ricans on the island, than other Hispanics, and than the United States population generally. Puerto Ricans in Puerto Rico have a diagnostic profile very similar to that of other U.S. residents, as shown by the results of the Puerto Rico Island Study and the ECA program. Puerto Ricans in New York experience greater socioeconomic pressures than other Hispanics and are one of the most disadvantaged ethnic groups in the United States (49). This correlation supports the social stress explanation for mental distress. Major idioms for expressing this distress continue to be the cultural syndromes of *nervios* and *ataques de nervios*. Future work to understand the mental health of the Puerto Rican community on the mainland and on the island of Puerto Rico will need to incorporate methods and concepts that will permit examination of cultural categories of distress and social status variables in a more sophisticated way. In this sense, this review of Puerto Rican mental health points to future directions for cross-cultural psychiatric research that includes social and cultural variables as key aspects of epidemiological research.

This paper deals with the fundamental question of "normative uncertainty"—of whether differences in rates of disorder are due to levels of psychiatric illness or ways of responding to questions (50). We do not conclude that it is possible to produce a gold standard or a methodological improvement which will eliminate the problem. We suggest, rather, that culturally meaningful illness categories and idioms of distress produce typical syndromes of symptoms and experiences. This cultural influence will clearly affect responses to questions on psychiatric research interviews and the caseness criteria or norms on symptom checklists. Perhaps less obviously, it also affects responses to criterial questions for diagnostic instruments such as the DIS. Our response to this influence is not to throw up our hands in despair or to suggest the irrelevance of such categories as major depressive episode or panic disorder. Instead, this review suggests directions for epidemiological research that treat culture not as a confounding variable to be controlled and eliminated, but as an essential matrix of human experience to be explored through carefully designed research.

Cross-cultural research in psychiatry has repeatedly been faulted for its ethnocentricity (39, 51). Now it is clear that to be culturally valid, comparative epidemiological and clinical studies need to do more than to follow a rigorous model of translation, back-translation, semantic adjustment, and validation of instruments. Cross-cultural validity can occur only when indigenous categories of experience are incorporated into assessment schedules. Otherwise, research will remain a kind of colonial imposition of Western categories on experiences, some of which are shared but many of which differ in important ways.

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Auditory Hallucinations and Smaller Superior Temporal Gyral Volume in Schizophrenia

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Recent neuropathologic investigations in schizophrenia report smaller volume of medial temporal lobe structures. These findings are confirmed by preliminary magnetic resonance imaging (MRI) studies. Direct stimulation of lateral temporal lobe structures in the region of the superior temporal gyrus provokes hallucinations. The authors' MRI study of young schizophrenic patients demonstrates smaller volume of the superior temporal gyrus (an auditory association area) and of the left amygdala. Smaller size of the left superior temporal gyrus and left amygdala is not accounted for by smaller size of the overall brain or temporal lobe. Shrinkage of the left superior temporal gyrus is strongly and selectively correlated with severity of auditory hallucinations.

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Auditory hallucinations are a cardinal symptom of schizophrenia, but their cause is unknown. Anatomic localization of normal auditory function suggests possible pathology in the temporal lobe, an area already implicated as abnormal in this illness (1, 2). Post-mortem studies, for example, report smaller size of structures in the medial temporal lobe of schizophrenic patients (3–5). Interpretation of any neuropathologic study is complicated by possible artifacts due to agonal events and post-mortem preparation. As Johnstone (6) has pointed out, schizophrenia is a nonfatal disease with generally early life onset. Brains studied after death are therefore most likely to be obtained from older patients who have been ill for many years, so that aging and incidental findings may obscure essential pathology. Magnetic resonance imaging (MRI) of young schizophrenic patients during life can overcome some of these difficulties. Such studies demonstrate various changes within the temporal lobe (7–10). It is unclear whether these result from the overall reductions in brain volume reported in schizophrenia (3, 11). Studies by Penfield and Perot (12) have shown that electrical stimulation of the superior temporal gyrus (a lateral temporal region) elicits complex hallucinations.

Using MRI, we examined the volumes of both medial and lateral temporal target regions, as well as control structures, in the brains of schizophrenic patients and individually matched control subjects. Measures of overall brain and temporal lobe size were also obtained. We hypothesized that volumes of temporal lobe structures (but not of control structures or overall estimates) would be smaller in the schizophrenic patients.

METHOD

Subjects

The index group consisted of 15 men (10 black and five white) who met criteria for schizophrenia accord-

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ing to the Structured Clinical Interview for DSM-III-R (SCID) (13). Their mean±SD age was 30.6±4.6 years (range, 20–36 years). All had been previously hospitalized at least once for their illness but were currently living in the community and receiving outpatient treatment, including neuroleptic medications, in the Schizophrenia Research Clinic of Johns Hopkins Hospital. Mean years of education were 12.3±1.5, and mean height was 174.1±6.4 cm.

Fifteen control subjects were selected from employees of Johns Hopkins Hospital and members of the surrounding community. Control subjects were individually matched to schizophrenic patients on age (within 2 years), race, gender, years of education (within 2 years), and parental socioeconomic status according to the Hollingshead scale (14). Mean age, height, and years of education for control subjects were 30.7±5.4 years, 178.2±7.6 cm, and 12.8±1.2 years, respectively. Comparison with the schizophrenic patients showed no differences on these measures or on socioeconomic status. Two schizophrenic patients and one control subject were not right-handed.

After the study had been fully explained and informed consent obtained, inclusion and exclusion criteria for both patients and control subjects were assessed by examination, which included the SCID administered by a psychiatrist, and, for patients, medical record review. Exclusion criteria were identical to those of a recent study from our group (15), i.e., any history of CNS illness, head injury that had caused unconsciousness for more than 1 hour, headaches of sufficient severity to have led to medical consultation, heavy alcohol or street drug use in the last 12 months, oral steroid use in the preceding 3 months, and loss of 25% or more of original body weight in the past 12 months. No schizophrenic subject had received ECT. No control subject had a history of psychiatric illness or hospitalization.

Procedure

All subjects were examined with the same 1.5 Tesla General Electric Signa MRI scanner. An initial high-quality 3-mm sagittal series was used for slice orientation, by identifying the anterior commissure-posterior commissure line. We then acquired spin-lattice relaxation time (T_1)-weighted coronal slices, at 90° to the anterior commissure-posterior commissure line, beginning at the genu of the corpus callosum and extending posteriorly through the temporal lobe to the splenium (repetition time [TR], 800 msec; echo time [TE], 20 msec; 3-mm thick, interleaved slices; field of view, 20–24 cm). Finally, 5-mm thick proton- and spin-spin relaxation time (T_2)-weighted axial cuts were obtained through the entire brain, parallel to the anterior commissure-posterior commissure line, using imaging measures of TR 2500 msec, TE 30/80 msec, with 5-mm thick interleaved slices and a field of view of 20–24 cm. All images were acquired by using 256×256-pixel spatial resolution and were stored on 9-track magnetic tape. MRI images were rated on a VAX Station 3200 graphics work station. Data from MRI tapes were stored on either a cassette tape subsystem or an optical WORM disk. Direct display from magnetic tape was chosen to avoid differences introduced by film processing and to take maximum advantage of image data. Custom graphics were developed locally in ULTRIX (UNIX) and used X-windows software. Slices containing structures of interest were identified on MRI films. Corresponding images were then displayed on the graphics work station and interactively outlined. Areas so defined were summed across slices and multiplied by slice thickness to yield volumes. From the coronal slices, we assessed volumes of right and left temporal lobes, superior temporal gyrus, amygdala, and the third ventricle. Four nontemporal control regions were used: from the T_2-weighted axial cuts, areas of 1) midbrain and 2) pons were assessed, as well as 3) the entire brain volume from the vertex to the foramen magnum, and from the sagittal series, 4) midsagittal brain area. One subject's right superior temporal gyrus was not rated because of poor image quality. Inter- and intrarater (R.E.P. versus S.S.R.) reliabilities, determined by using intraclass correlations, were high (r>0.86 for all regions). Validity of volumetric measures was estimated with a realistic anatomic phantom, scanned on the same MRI scanner, and with parameters identical to those of our subjects. Correlation of actual and estimated volumes was excellent (r>0.92).

MRI ratings were made by a neuropathologist (R.E.P.) who was familiar with temporal lobe anatomy and blind to diagnosis, according to the following criteria.

Superior temporal gyral volume. Cortex and white matter were measured in three consecutive coronal levels (two with measured amygdala, plus the next anterior level). The cortex and white matter are bounded laterally by the superior temporal sulcus, medially by the lateral sulcus, and inferiorly by a line connecting the depth of the superior temporal sulcus and the circular sulcus of the insula.

Amygdala volume. Gray matter region was measured in two coronal levels of rostromesial temporal lobe, with the inferior horn of lateral ventricle or white matter as the inferior boundary, white matter as the lateral and superior boundary, and the cortical surface as the medial boundary. Medial amygdala includes portions of uncal cortex. Two consecutive levels where amygdala appeared the largest were measured.

Third ventricle volume. The midline ventricle was defined in two consecutive coronal levels between the anterior commissure and the mammillary bodies, bounded laterally and inferiorly by the hypothalamus and superiorly by the fornix.

Midbrain area. All portions of brain stem were measured from one axial cut taken at about the level of the red nucleus, where the cerebral aqueduct and interpeduncular fossa are readily identified.

Pons area. All portions of brain stem were measured in a single axial slice from above the brachium pontis,

TABLE 1. Regional Volumes of Temporal Lobe Structures in Schizophrenic (N=15) and Control (N=15) Subjects

Regional Measure	Schizophrenic Subjects		Normal Control Subjects					Difference Between Schizophrenic and Control Subjects (%)
	Mean	SD	Mean	SD	t	df	p	
Target regions								
Superior temporal gyrus (mm^3)								
Left	2,049	318	2,289	304	2.89	14	0.01[a]	−11.1
Right	2,032	331	2,314	422	2.56	13	<0.05	−13.0
Amygdala (mm^3)								
Left	1,410	133	1,536	154	3.27	14	<0.01[a]	−8.6
Right	1,342	226	1,454	170	1.54	14	n.s.	−8.0
Third ventricle (mm^3)	313	109	219	54	2.62	14	<0.05	+35.0
Control regions								
Pons area (mm^2)	3,239	424	2,980	647	1.03	14	n.s.	+8.3
Midbrain area (mm^2)	3,712	703	3,326	698	1.20	14	n.s.	+11.0
Midsagittal brain area (mm^2)	132,167	697	131,227	1,367	0.26	14	n.s.	+0.7
Overall brain volume (cc)	1,245	145	1,270	115	0.64	14	n.s.	−2.0
Whole temporal lobe (mm^3)								
Left	30,182	4,860	32,514	3,670	1.95	14	n.s.	−7.2
Right	30,838	4,674	34,098	4,064	2.36	14	<0.05	−10.0

[a] Significant at $p<0.05$ with the Bonferroni correction.

where the basis pontis and fourth ventricle are clearly defined.

Temporal lobe volume. Combined gray and white matter volumes were measured in nine (3-mm thick) coronal levels of temporal lobe in all cases. Volume was summed from the two levels rostral to the first slice with amygdala, the two levels with amygdala, and the subsequent five posterior levels of temporal lobe. Gyral outlines defined lateral and inferior boundaries; superior was the sylvian fissure. Anterior to the limen insulae, superior and medial boundaries were gyral outlines. Posterior to the limen insulae, medial boundaries were lines drawn from the depths of the circular sulcus to either the lateral tip of the hippocampal or endorhinal fissure and then along the contour of the mesial temporal surface. Volume of the inferior horn of the lateral ventricle was excluded.

Midsagittal area. A single midsagittal section was measured in the plane where the cerebral aqueduct was identified. The cortical gyral pattern was outlined in the frontal, parietal, and occipital lobes. The inferior margin was a line from the posterior inferior aspect of the gyrus rectus to the inferior portion of the splenium of the corpus callosum, continued across the parieto-occipital isthmus and along the lingula of the occipital lobe.

Whole brain volume. All (5-mm) axial views were examined. All of the frontal, temporal, parietal, and occipital cortex was outlined, and the volume of cortex, white matter, and ventricles was summed.

Before rating scans in the current series, we tabulated the previous anatomic definitions in an atlas, with corresponding annotated coronal MRI images (obtainable from the authors on request).

Schizophrenic symptoms present during the patient's most recent exacerbation were assessed by chart review and rated retrospectively by two individuals, who were blind to MRI measurements, on the Scale for the Assessment of Positive Symptoms (16) and the Scale for the Assessment of Negative Symptoms (17).

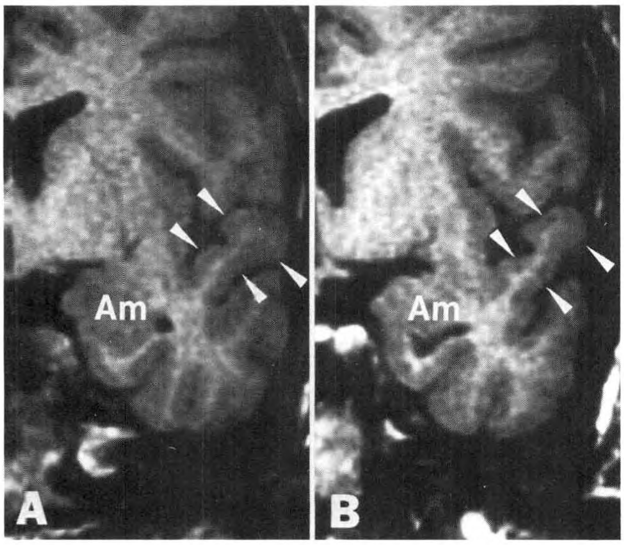
RESULTS

We first examined target regions. As shown in table 1, schizophrenic patients had smaller superior temporal gyri bilaterally, smaller left amygdalas, and larger third ventricles on MRI than the matched control subjects. We next compared nontarget regions, including all control structures and overall volumes. None were significantly different, except for the right temporal lobe, before the Bonferroni correction, and none after. The observed total of five of 11 significant comparisons in table 1 is many times greater than the 0.55 predicted by chance expectation (exact binomial test: $p=0.0002$, two-tailed).

Representative superior temporal gyri of one control subject and one matched schizophrenic patient are illustrated in figure 1. Twelve (80%) of the schizophrenic patients had smaller left superior temporal gyri, 11 (73%) had smaller right superior temporal gyri, 11 (73%) had smaller left amygdala, 10 (67%) had smaller right temporal lobes, and 11 (73%) had smaller third ventricles than matched control subjects.

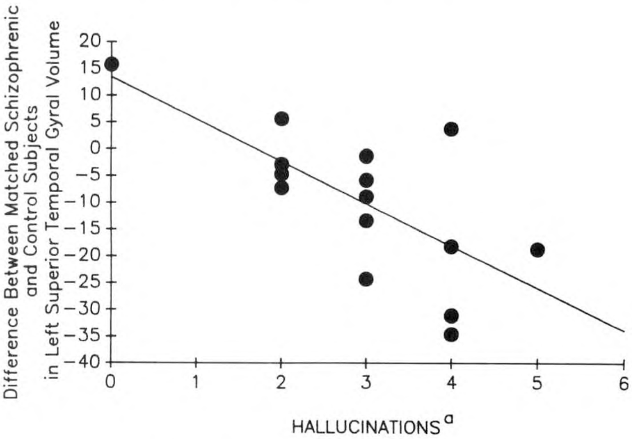
The whole brain was 2% smaller in patients than in control subjects, the left temporal lobe was 7.7% smaller, and the right temporal lobe was 10% smaller. We wished to examine whether the observed smaller size of left amygdala and both superior temporal gyri could be accounted for by differences in overall brain or temporal lobe volume. In an analysis of covariance comparison using overall brain volume as a covariate, the slopes of the regression lines relating left amygdala volume to overall brain volume were significantly

FIGURE 1. Portions of T_1-Weighted Coronal MRIs of Brains of a Control (A) and a Schizophrenic (B) Subject[a]



[a] The superior temporal gyrus (arrowheads) is measured at the level of the amygdala (Am).

FIGURE 2. Correlation Between Severity of Hallucinations and Percent Difference in Left Superior Temporal Gyral Volume Between Schizophrenic (N=15) and Control (N=15) Subjects



[a] Measured with the Scale for the Assessment of Positive Symptoms; $r=0.70$, $df=14$, $p<0.005$.

different between schizophrenic and control groups ($F=5.52$, $df=1, 26$, $p<0.05$). Similar results were found for the left amygdala volume with the left temporal lobe volume as a covariate ($F=5.05$, $df=1, 26$, $p<0.05$), left superior temporal gyral volume with brain volume as covariate ($F=8.16$, $df=1, 26$, $p<0.01$), and left superior temporal gyral volume with left temporal lobe volume as covariate ($F=5.97$, $df=1, 26$, $p<0.05$), but not for right superior temporal gyral volume with brain volume as covariate ($F=2.36$, $df=1, 26$, n.s.) or for right superior temporal gyral volume with right temporal lobe volume as covariate ($F=0.18$, $df=1, 26$, n.s.) These results suggest that while right superior temporal gyral volume differences may result from differences in overall brain or same-side temporal lobe volumes, the differences between schizophrenic and control subjects in left amygdala and left superior temporal gyral volumes do not.

We next looked for the possibility that smaller volumes in the superior temporal gyrus or amygdala were lateralized, by using multivariate analysis of variance to search for significant interactions of side with diagnosis. None were found. (For superior temporal gyrus, $F=0.20$, $df=1, 27$, n.s.; for amygdala, $F=0.05$, $df=1, 28$, n.s.) For superior temporal gyrus, we confirmed a significant effect of diagnosis.

We then examined whether any regional change was correlated with schizophrenic symptoms. Percent difference in volumes for regions reaching significance in table 1 were calculated for each matched schizophrenic/control pair, using the formula $[(\text{schizophrenic volume minus control volume}) \div 0.5 \times (\text{schizophrenic} + \text{control volume})] \times 100$. Using Pearson correlation coefficients, we compared these percentage differences with scores on the Scale for the Assessment of Positive Symptoms and the Scale for the Assessment of Negative Symptoms (p values adjusted by Bonferroni correction to <0.005 because of multiple comparisons). Only one significant relationship emerged, as shown in figure 2. There was a positive correlation between percent difference in left superior temporal gyral volume and global hallucination severity score on the Scale for the Assessment of Positive Symptoms ($r=0.70$, $N=15$, $p<0.005$), so that greater size reductions were associated with greater severity of hallucinations. When these calculations were repeated for the remaining regions, similar but weaker correlations were noted. For the left and right superior temporal gyrus, left and right amygdala, and third ventricle percentage difference scores, respectively, correlations with total score on the Scale for the Assessment of Positive Symptoms, total score on the Scale for the Assessment of Negative Symptoms, and the Scale for the Assessment of Positive Symptoms hallucinations, delusions, and thought disorder subscales were 0.14, 0.44, 0.03, −0.07, and −0.05; 0.40, −0.12, 0.14, −0.34, and 0.14; 0.70, −0.07, 0.41, −0.31, and 0.29; −0.51, −0.10, −0.20, 0.48, and −0.18; and −0.05, 0.48, −0.05, −0.06, and −0.03. We analyzed the relationship in figure 2 more closely. The Scale for the Assessment of Positive Symptoms uses separate hallucination items to arrive at a global hallucination severity score. We correlated left superior temporal gyrus percent difference scores with the separate ratings for auditory ($r=0.71$, $N=15$, $p<0.005$), somatic/tactile ($r=0.04$, $N=15$, n.s.), visual ($r=0.44$, $N=15$, n.s.), and olfactory ($r=0.00$, $N=15$, n.s.) hallucinations. The only significant correlation after correction for multiple comparisons was with auditory hallucinations.

DISCUSSION

Many researchers have reported nonspecific brain alterations in schizophrenia. More recently, attention has focused on the temporal lobe. It is not yet clear if the entire temporal region is affected or only specific portions of it. Also unknown is how such changes relate to typical symptoms of schizophrenia. We report several structural changes in the temporal lobes of schizophrenic patients, one of which correlates with the presence of a principal symptom. Andreasen et al. (11) and Pearlson et al. (15) have both reported that schizophrenic patients have smaller brains than control subjects. Many apparent regional size reductions in previous studies of schizophrenia that did not correct for total brain volume may thus reflect diffuse rather than localized brain atrophy. A recent study from our group (15) suggested that socioeconomic status is a significant correlate of brain size. In the current study, we matched subjects directly on socioeconomic status and indirectly on height and detected no patient versus control differences in two measures of overall brain size (midsagittal brain area and whole brain volume).

Certain caveats must be borne in mind regarding this report. For example, all of our patients were men, and all were medicated with neuroleptics. Evaluation of symptoms was retrospective, using the Scale for the Assessment of Positive Symptoms (which was designed as an interview scale). The specificity of our anatomic findings is unknown, and work is currently underway in order to determine whether manic-depressive patients with auditory hallucinations and schizophrenic women show similar structural abnormalities. Strengths of the study include careful individual matching of patients and control subjects and attempts to account for effects of diffuse brain atrophy.

Our report is in agreement with other studies showing less specific structural abnormalities in schizophrenia. The sylvian fissure overlies the superior temporal gyrus and expands as the gyrus shrinks; measurements from computed tomographic studies show enlargement of this fissure (18). Like other investigators (19), we found a significant (but probably nonspecific) increase in third ventricular volume, as well as decreased size of a mesial temporal structure, the amygdala (4, 5). One report (20) noted asymmetries of amygdala dopamine distribution in schizophrenia, with left-sided increases. We did not assess the hippocampus or parahippocampal gyrus in this report, areas implicated in schizophrenia by others (3, 4, 8). Our results are consistent with the report of Suddath et al. (7), who showed bilateral reductions in overall temporal lobe gray matter, and also with that of Jakob and Beckmann (21), who observed "deviations of the sulcogyral pattern in the left temporal lobe" in 42 of 64 schizophrenic subjects.

The specific area of the superior temporal gyrus that we measured corresponds to auditory association cortex area 22 in the Brodmann nomenclature (22). Small segments of areas 41, 42, and 52 were also included. Penfield and Perot (12) electrically stimulated multiple cortical and subcortical areas in both hemispheres of epileptic subjects and found that complex auditory hallucinations were elicited only in the vicinity of the superior temporal gyrus. That study also elicited other mental experiences reminiscent of schizophrenia: "alteration in the apparent meaning of things seen or heard," "false interpretations of the present," and "illusional emotions." Auditory hallucinations could be elicited from either hemisphere but were more frequently observed after left-sided stimulation, which is consistent with our current data.

Our findings are also consistent with reports of physiological abnormalities in schizophrenia. The P300 auditory evoked response is believed to originate in the vicinity of the superior temporal gyrus (23), and abnormalities in the left-sided P300 correlate with both score on the Scale for the Assessment of Positive Symptoms and sylvian fissure enlargement (24, 25). Magnetoencephalography shows that the M100 EF component of the left auditory evoked field of schizophrenic patients is abnormal (26); its generator is located in the supratemporal plane. Our anatomical findings in this area may therefore suggest the substrate for evoked response abnormalities in schizophrenia. The precise relationship between these neurophysiologic changes, the anatomic findings, and clinical symptoms will be elucidated by further studies.

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A Discriminant Validity Study of Negative Symptoms With a Special Focus on Depression and Antipsychotic Medication

Richard R.J. Lewine, Ph.D.

If the construct validity of the negative symptom syndrome is to be established, the conceptual and operational overlap between negative symptoms and other syndromes such as depression and the effects of medication must be explained. The author assessed 26 patients with schizophrenia and 21 patients without schizophrenia, most of whom had depression, at the end of an average 2-week drug washout period and after approximately 2 months of psychotropic medication administration. Negative symptoms were remarkably consistent in patients with schizophrenia despite pharmacological intervention. In contrast, the patients without schizophrenia manifested significant decreases in negative symptoms.

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Negative symptoms, generally conceptualized as representing the loss of normal function (1–3), have assumed a prominent role in the biological study of schizophrenia. Kraepelin (4) specifically offered the "annihilation of the will" as the fundamental schizophrenic deficit, with its etiology firmly rooted in neurological dysfunction. Reviews of substantive findings suggest that negative symptoms, especially when contrasted to positive symptoms, are associated with poor premorbid development, enlarged lateral ventricles, neuropsychological impairment, a prominent genetic component, and poor treatment response (5, 6).

Although the content and predictive validity of negative symptoms have been addressed with regularity and some consistency of results, the evidence for discriminant validity has been far more uncertain (5). One important problem is the conceptual and operational overlap among negative symptoms, depressive symptoms, and global psychopathology (7). Another constraint, often dictated by practical considerations, is the frequent use of a single rater to fill out multiple scales for an individual patient, thereby potentially increasing artificially the discriminant power of negative symptoms. Finally, antipsychotic medications may also directly dampen hedonic capacity, thereby causing or exacerbating negative symptoms, and may indirectly mimic negative symptoms in the form of extrapyramidal side effects (especially akinesia).

In this discriminant validity study I will attempt to address the three issues of operational overlap, medication effect, and rater contamination by including the following design features: repeated measurements while subjects were receiving medication and while they were medication free, a comparison group of psychiatric patients without schizophrenia (most of whom were depressed), and different raters for the assessment of syndromes similar to negative symptoms. This study provides a strong test of the validity of the negative symptom construct in schizophrenia.

METHOD

The subjects for this study were drawn from consecutive admissions to two 22-bed inpatient research units. Written, informed consent to participate was obtained from 108 patients; 12 of these patients served in the training phase of the study, leaving 96 who participated in the formal study. Of these 96 patients, 84 (87.5%) were assessed at least once (although complete data sets were not available for all of them); the remaining 12 (who did not differ significantly in sociodemographic characteristics from the 84 who participated) withdrew consent, were clinically untestable because of psychosis exacerbation, or were generally uncooperative.

Each patient received a discharge consensus *DSM-III* diagnosis based on all available historical and clinical information but completely blind to the formal ratings. Assessments from both a 2-week medication washout period and after approximately 2 months of psychotropic medication administration were available for 26 patients with schizophrenia and 21 patients without schizophrenia. The sociodemographic characteristics of these 47 patients are summarized in table 1. There were significantly fewer white patients in the group with schizophrenia, and these patients had a

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TABLE 1. Demographic and Clinical Characteristics of Psychiatric Patients With or Without Schizophrenia

Characteristic	Patients With Schizophrenia (N=26)	Patients Without Schizophrenia (N=21)
Sex		
Men		
Number	22	17
Percent	85	81
Women		
Number	4	4
Percent	15	19
Race[a]		
White		
Number	12	18
Percent	46	86
Other		
Number	14	3
Percent	54	14
Current age (years)		
Mean	27.4	30.3
SD	6.0	8.4
Age at onset of illness (years)[b]		
Mean	21.9	21.7
SD	5.8	7.5
Age at first hospital admission (years)		
Mean	24.7	25.3
SD	5.9	7.8
Number of hospitalizations		
Mean	2.1	2.7
SD	4.6	2.5
Socioeconomic status[c]		
Mean	101.1	80.8
SD	25.9	33.4
Premorbid competence score[d]		
Mean	2.3	2.7
SD	0.8	0.9

[a] $Z=2.837$, $p<0.003$.

[b] N=24 for patients with schizophrenia.

[c] $t=2.375$, $df=45$, $p<0.05$, two-tailed t test.

[d] Scores range from 1 (low) to 5 (high) and represent the means of ratings for age, education, occupational level, employment history, and age at first hospitalization.

significantly lower mean socioeconomic status than the patients without schizophrenia in the repeat measures subgroup. However, neither race nor socioeconomic status had significant effects on negative symptoms. The diagnoses of the patients without schizophrenia were major depression (N=7), schizoaffective disorder with prominent depression (N=7), bipolar mania (N=3), hypochondriasis (N=1), borderline personality disorder (N=1), obsessive-compulsive disorder (N=1), and psychotic disorder not otherwise specified (N=1).

Negative symptoms were evaluated by using the Scale for the Assessment of Negative Symptoms (1, 8). To assess syndromes from which negative symptoms were to be differentiated, the Hamilton Rating Scale for Depression (9), the Global Assessment Scale (GAS) (10), and the Simpson-Angus Scale for rating extrapyramidal side effects (11) were used.

The study design called for an initial medication washout period of 2–4 weeks, at the end of which baseline measures were taken. Repeated measures were scheduled for approximately 5 and 10 weeks after the initiation of psychotropic medication administration.

To counter the potential rater contamination in contrasting the different syndromes, it was critical that different raters be used for the various scales so that the relationships among the scales purporting to measure different constructs would not unintentionally be determined by rater expectations. Therefore, different raters completed the Scale for the Assessment of Negative Symptoms, the Hamilton depression scale, and the Simpson-Angus Scale for rating extrapyramidal side effects.

RESULTS

Reliability on the Scale for the Assessment of Negative Symptoms was excellent, especially for the global score (the sum of the component global subscales). Intraclass correlations (ICCs) for the various components ranged from 0.65 (alogia) to 0.82 (inattention); the global sum score had an ICC of 0.91. Interrater reliabilities were excellent for the Simpson-Angus Scale (0.92) and the total Hamilton depression scale score (0.82) as well.

All 26 of the patients with schizophrenia were treated with antipsychotic medications, usually chlorpromazine (15 [57.7%] of the patients) or trifluoperazine (10 [38.5%] of the patients); 11 (52.4%) of the patients without schizophrenia were also treated with antipsychotic medications in addition to their other medications. Patients with and without schizophrenia did not differ significantly in mean washout period, which was 15.5±6.2 days for those with schizophrenia and 13.9±4.0 days for those with nonschizophrenic psychiatric disorders. Nor did they differ in the mean number of days between washout and final assessment while they were receiving medications, which was 79.6±19.6 days for the patients with schizophrenia and 77.6±25.4 days for those without schizophrenia. The final mean doses (in chlorpromazine equivalents) (12) for the patients with schizophrenia (1341.2±910.9 mg/day) and those without schizophrenia (1319.0±2253.7 mg/day) who were receiving antipsychotics did not differ significantly.

We conducted a series of two (Diagnoses) by two (Time—while receiving medications versus while not receiving medications) repeated measures analyses of variance (ANOVAs). We used multiple ANOVAs rather than an initial multiple analysis of variance because we were interested, a priori, in the behavior of the individual scales over time. This, of course, raises the risk of type I errors. Given a level of significance of 0.05, we can conservatively estimate finding fewer than two significant effects by chance in this analysis; in fact, six were obtained.

The patients' scores on the different measures of negative symptoms, depression, global symptoms, and

TABLE 2. Negative Symptoms, Depression, Global Symptoms, and Extrapyramidal Side Effects in Psychiatric Patients With or Without Schizophrenia Before and During Drug Treatment

		Score at End of Drug Washout		Score After Drug Treatment[a]	
Scale	N	Mean	SD	Mean	SD
Scale for the Assessment of Negative Symptoms					
Schizophrenic patients	21	11.9	3.9	11.8	6.2
Nonschizophrenic patients	15	8.8	4.9	5.4	4.9
Hamilton Rating Scale for Depression					
Schizophrenic patients	26	13.3	6.0	11.0	6.6
Nonschizophrenic patients	20	21.7	11.6	15.8	12.9
GAS					
Schizophrenic patients	26	35.2	9.1	46.2	15.3
Nonschizophrenic patients	16	38.9	15.1	49.4	19.2
Simpson-Angus Scale					
Schizophrenic patients	26	7.1	8.6	7.7	7.1
Nonschizophrenic patients	15	4.3	5.7	4.5	6.3

[a] All of the patients with schizophrenia were taking antipsychotic medications; 11 of the patients without schizophrenia were taking antipsychotics in addition to their other medications.

extrapyramidal side effects after the drug washout period and while receiving medications are summarized in table 2.

There was a significant main effect of Diagnosis (F=9.60, df=1, 34, p=0.004) and Time (F=5.22, df=1, 34, p=0.029) and a significant Diagnosis by Time interaction (F=4.17, df=1, 34, p=0.049) according to scores on the Scale for the Assessment of Negative Symptoms. Patients with schizophrenia not only had significantly higher Scale for the Assessment of Negative Symptoms ratings than patients without schizophrenia but also failed to show any decrement in rating over time, in contrast to the patients without schizophrenia, who exhibited a marked reduction in their mean negative symptom rating.

The patients without schizophrenia had higher overall mean scores on the Hamilton depression scale than the patients with schizophrenia (F=7.39, df=1, 44, p=0.009), and both groups had a reduction in depression scores over time (F=8.59, df=1, 44, p=0.005); the interaction between Diagnosis and Time was not significant.

According to GAS scores, the improvement in global functioning between the end of the washout period and after medication had been administered for approximately 2 months was significant for both groups (F=6.06, df=1, 39, p=0.018), and there were no other significant effects. In other words, both patient groups improved equally and significantly.

According to Simpson-Angus Scale ratings of extrapyramidal side effects, neither main nor interaction effects were significant (Time, F=0.110, df=1, 41, p=0.737; Diagnosis, F=2.17, df=1, 14, p=0.148; and Time by Diagnosis, F=0.03, df=1, 41, p=0.875).

In sum, patients with schizophrenia were statistically different from those without schizophrenia in having a higher mean rating on the Scale for the Assessment of Negative Symptoms and a lower mean rating for depression. The negative symptoms did not change significantly from washout to after medication administration in the patients with schizophrenia. In contrast, the change in Scale for the Assessment of Negative Symptoms scores over time reflected significant improvement in the patients without schizophrenia. The two groups did not differ significantly in overall severity of disorder or in extrapyramidal side effects.

DISCUSSION

The patients with schizophrenia could be clearly discriminated from those without schizophrenia on the basis of negative symptoms and signs; however, they did not differ significantly from the nonschizophrenic psychiatric patients in either global severity or extrapyramidal side effects. The schizophrenic patients had significantly lower depression scores. This study provided a particularly stringent test of interdiagnostic group discriminant validity because most of the patients without schizophrenia had psychotic depression and schizoaffective disorder.

These data are consistent with most of the empirical literature examining interdiagnostic differences (1, 13, 14) as well as the relationship between depression and negative symptoms in schizophrenia (15, 16). Berenbaum et al. (13), in particular, used a comparison group of patients with pure depression and found that schizophrenic patients had a significantly higher mean score on emotional blunting, especially weighted by avolition, than did depressed patients. The major exception to this trend is a study by Kulhara and Chadda (17), who found that patients with major depressive disorder diagnosed according to Research Diagnostic Criteria had significantly higher scores than patients with schizophrenia on most items of the Scale for the Assessment of Negative Symptoms. The major exceptions, that is, items on which the patients with schizophrenia had higher mean scores, included poor eye contact, inappropriate affect, and thought blocking. Since there are no obvious methodological factors that could account for this inconsistency in findings, cultural factors are implied (the Kulhara and Chadda study was conducted in India).

Interpretations of medication effects from these data must be made cautiously because the medication effect was completely confounded with time. That is, medication always followed washout. The "washout" itself was constrained by its relative brevity (about 2 weeks) and the uncertainty about the effects of long-term maintenance medication. With this caveat, the data suggest that medication/time had very little effect on the mean level of negative symptoms in patients with schizophrenia, as has been reported by Kay et al. (18, 19). This was not a general failure to respond, however, because the schizophrenic patients did show significant clinical improvement over time as measured by the GAS and Hamilton depression scores. The consistency of negative symptoms in the face of time and medication is striking; a similar picture was painted by Pogue-Geile and Harrow (20) in their 2-year after-discharge follow-up study.

It would appear, therefore, that studies of negative symptoms in patients and using procedures like those in this study are unlikely to be affected substantially by medication over the short-term, a methodological point that has been of some concern. If possible, other studies must determine the impact of long-term antipsychotic use and explore further the suggestion that anticholinergics produce negative-like symptoms (21).

The pattern of results for the 21 patients without schizophrenia differs strikingly from that for the 26 patients with schizophrenia. Whatever is being measured by negative symptom rating scales in these patients, it changes substantially with time/medication. I am reminded here of the differences in correlational patterns suggesting that negative symptoms may reflect an affective syndrome in female schizophrenic patients and the traditional amotivational syndrome in men (5, 22). It may be that use of negative symptom rating scales in clinical populations with prominent affective features (female patients with schizophrenia, patients with schizoaffective disorder, or patients with affective disorders) is misleading.

Negative symptoms in the 26 patients with schizophrenia seemed clearly differentiable from symptoms of depression. Depression, if anything, was reduced after an average of more than 2 months of antipsychotic treatment. The results of this study provide strong evidence for the validity of the negative symptom syndrome as operationalized in the Scale for the Assessment of Negative Symptoms. In this group of patients, such symptoms seemed remarkably resistant to change, despite pharmacological intervention.

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Plasma Norepinephrine in Chronic Schizophrenia

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Several lines of evidence indicate altered noradrenergic function in schizophrenia. The authors examined resting, standing, and change (standing minus resting) in plasma norepinephrine levels in 14 drug-free patients with chronic schizophrenia or schizoaffective disorder and in 33 age- and sex-matched healthy volunteers. Schizophrenic patients had significantly higher resting and standing plasma norepinephrine levels and significantly greater change. Resting and standing levels were significantly related to positive and negative symptoms. There was a significant positive correlation between resting plasma and CSF norepinephrine levels and a significant negative correlation between CSF homovanillic acid and resting, standing, and change in plasma norepinephrine levels.

(Am J Psychiatry 1990; 147:1467–1470)

Several lines of evidence suggest that schizophrenia is associated with altered noradrenergic function. Postmortem studies (1–5) have revealed above-normal levels of norepinephrine and its metabolites in several brain regions, including the nucleus accumbens and selected cortical areas. In addition, several but not all studies of this subject have reported above-normal levels of norepinephrine and/or its metabolites in CSF (6–12) and plasma (10, 13–16). Moreover, the noradrenergic α_2 agonist clonidine suppresses plasma 3-methoxy-4-hydroxyphenylglycol (MHPG), a major norepinephrine metabolite, in control subjects but not in schizophrenic patients (17), and the noradrenergic α_2 receptor antagonist yohimbine increases plasma MHPG in a subgroup of schizophrenic patients (18). These data support the hypothesis of subsensitive α_2 receptor function in at least a subgroup of schizophrenic patients. Furthermore, several antipsychotic agents (e.g., clozapine) have potent effects on noradrenaline receptors (19). The significance of altered noradrenergic function for the pathophysiology of schizophrenia remains unclear.

A relatively simple approach to assessing noradrenergic function in clinical populations is determining resting and standing plasma norepinephrine levels and the change between them (standing minus resting). Resting plasma levels provide information about basal sympathetic nervous system activity. Several studies have shown that standing leads to a significant elevation in plasma norepinephrine, which is a result of the complex sympathetic nervous system response to orthostasis (20–22). Thus, standing plasma level and the change in plasma level provide an index of sympathetic nervous system regulation. Moreover, although norepinephrine does not readily cross the blood-brain barrier (23–25), significant correlations between CSF and plasma norepinephrine levels have been reported (26, 27), suggesting that plasma norepinephrine levels may reflect aspects of CNS processes and/or that under some circumstances CSF levels are controlled by the same process driving sympathetic nervous system activity (28).

In the present study, we examined resting plasma norepinephrine levels, standing levels, and change values in drug-free schizophrenic patients and age- and sex-matched healthy comparison subjects. In addition, we assessed the relationship between plasma norepinephrine level and schizophrenic psychopathology and the relationship between plasma norepinephrine level and CSF levels of norepinephrine and the dopamine metabolite homovanillic acid (HVA).

METHOD

Fourteen inpatients who fulfilled the *DSM-III* criteria for schizophrenia or schizoaffective disorder and 33 healthy volunteers participated in the study. The patient group comprised eight men and six women, and they had a mean±SD age of 28±6 years. These patients had chronic courses before admission: 9±7 years of illness and 7±8 prior psychiatric hospitalizations. They were free of all active medication and were receiving placebo in a double-blind fashion when they participated in the study. Twelve patients had been neuroleptic free for at least 3 weeks before participa-

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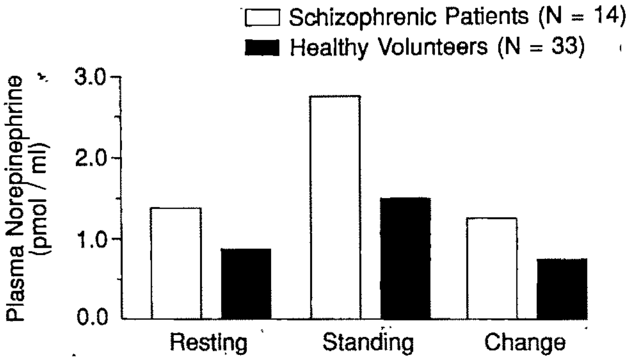
FIGURE 1. Mean Plasma Norepinephrine Levels of Patients With Schizophrenia and Age- and Sex-Matched Comparison Subjects[a]



[a] Significant differences between schizophrenic patients and healthy volunteers for resting (mean±SD=1.4±0.7 versus 0.7±0.3; t=4.4, df=45, p<0.0001), standing (2.7±1.1 versus 1.5±0.6; t=5.2, df=45, p<0.0001), and change (standing minus resting) (1.3±0.8 versus 0.7±0.4; t=3.1, df=45, p=0.004).

tion, one patient had been neuroleptic free for 14 days, and one patient had been drug free for 8 days.

The volunteers were matched for age (mean±SD: 28±7 years) and sex (20 men and 13 women). They had no lifetime history of psychiatric illness, as determined from interviews following the Schedule for Affective Disorders and Schizophrenia—Lifetime Version (SADS-L) (29), and no family history of psychiatric illness. A physical examination, ECG, and blood workup of each patient indicated no medical illnesses. They were taking no medications at the time of the study.

The patients and volunteers were maintained on a low-monoamine, caffeine-restricted diet. After an overnight fast, a butterfly needle with a heparin lock was inserted in the antecubital fossa at 8:30 a.m. The subjects remained at bed rest for the subsequent 30 minutes. At 9:00 a.m., 6 ml of blood was drawn. The subjects then stood at the bedside for 5 minutes. A second blood sample was then taken. Both the resting and standing blood samples were immediately placed on ice after drawing. Plasma was separated in a refrigerated centrifuge within 20 minutes of drawing, and the samples were stored at −70 °C until assaying. Norepinephrine levels were determined by means of high-pressure chromatography with electrochemical detection (30).

Research psychiatrists blind to medication status performed ratings for the week of the plasma norepinephrine test to determine 1) the sum of the Brief Psychiatric Rating Scale (BPRS) (31) scores for positive symptoms: hallucinatory behavior, unusual thought content, distractibility, and conceptual disorganization (N=13), and 2) the Abrams and Taylor Scale for Emotional Blunting (32) total score for negative symptoms (N=14).

Eleven of the 14 (drug-free) patients had lumbar punctures during the same period as the plasma norepinephrine determinations. CSF levels of norepinephrine and HVA were determined by means of high-pressure liquid chromatography with electrochemical detection (33). We have previously given a more detailed description of the lumbar puncture procedure and assaying techniques (16, 34).

TABLE 1. Relationship Between Plasma Norepinephrine Levels and Positive/Negative Symptoms in 14 Schizophrenic Patients

	Correlation (r) With Plasma Norepinephrine Level					
	Resting Level			Standing Level		
Symptom Measure	r	df	p	r	df	p
BPRS positive symptom score	0.54	11	0.05	0.65	12	≤0.01
Abrams-Taylor negative symptom score	0.72	12	≤0.01	0.50	12	0.07

Nonpaired t tests were used to determine differences between the schizophrenic patients and volunteers, Pearson's correlation coefficient was used for correlative analyses, and stepwise multiple regression was used to assess relationships among variables. All tests were two-tailed.

RESULTS

Compared to the volunteers, the schizophrenic patients had a significantly higher mean resting plasma norepinephrine level, a significantly higher standing level, and significantly greater change between standing and resting values (see figure 1). There were significant relationships between the resting and standing plasma norepinephrine levels and the BPRS positive symptom score and Abrams-Taylor negative symptom score (see table 1). Change in plasma norepinephrine levels was not correlated with the symptom measures. A stepwise multiple regression was used to assess the relationship between positive and negative symptoms in predicting resting plasma norepinephrine level. Negative symptoms entered at step 1 (multiple R=0.73, F=12.7, df=1, 11, p=0.004), and positive symptoms failed to contribute significantly at step 2 (multiple R=0.75, F=0.61, df=2, 10, p=0.45), suggesting that positive and negative symptoms did not make additive contributions in predicting plasma norepinephrine levels.

There was a significant positive correlation between CSF norepinephrine levels (mean±SD: 0.60±0.31 pmol/ml) and resting plasma levels (r=0.59, df=9, p=0.03), but plasma norepinephrine standing and change values were not correlated with CSF norepinephrine levels. Moreover, there were significant negative correlations between CSF HVA (mean±SD: 155.8±78.1 pmol/ml) and plasma norepinephrine resting levels (r=−0.64, df=9, p=0.02), standing levels (r=−0.70, df=9, p=0.009), and change values (r=−0.50, df=9, p=0.06). A stepwise multiple regression was used to assess the relationship between CSF HVA and CSF norepinephrine in predicting resting plasma norepinephrine levels. CSF HVA entered at step 1 (multiple R=0.64, F=6.4, df=1, 9, p=0.03). At step 2, CSF norepinephrine contributed additively to CSF HVA in predicting plasma norepinephrine at a level approaching significance (multiple R=0.77, F=3.4, df=2, 8, p=0.1). CSF norepinephrine and HVA were not significantly correlated with the negative and positive symptom ratings.

DISCUSSION

The results of this study indicate that patients with schizophrenia or schizoaffective disorder, in comparison to healthy volunteers, have higher resting plasma norepinephrine levels, higher standing levels, and greater change from resting to standing. Other authors have reported that schizophrenic patients have above-normal plasma norepinephrine levels (10, 13, 15). Castellani et al. (13) found that standing plasma norepinephrine levels and supine and standing pulse rates were significantly above normal in schizophrenic patients. Studies of depressed patients have also revealed high levels of plasma norepinephrine and its metabolites (21, 22), suggesting there may be aspects of noradrenergic dysfunction that are common to both schizophrenia and affective illness. The significance of plasma norepinephrine levels for the pathophysiology of schizophrenia is unclear. We found significant correlations between plasma norepinephrine levels and positive and negative symptoms, suggesting that greater noradrenergic activity may be related to primary schizophrenic psychopathology. In addition, it has been suggested that plasma norepinephrine reflects arousal, and greater arousal is a commonly described correlate of psychosis and negative symptoms (12, 15, 21, 35–37). Thus, high levels of plasma norepinephrine may be related to an interaction between primary schizophrenic symptoms and arousal. The data relating plasma norepinephrine to positive and negative symptoms agree with our recent report of a significant relationship between plasma MHPG and negative symptoms (16) and other studies demonstrating a relationship between noradrenergic function and schizophrenic symptoms (6, 12, 38). Moreover, several studies have demonstrated a relationship between plasma HVA and schizophrenic psychopathology (39–44). Since plasma HVA, like plasma norepinephrine, is derived largely from the peripheral sympathetic nervous system (45), it is possible that plasma HVA and plasma norepinephrine are reflecting aspects of a common alteration in schizophrenia; we will examine this issue in future studies. Our failure to find a significant relationship between CSF norepinephrine levels and positive and negative symptoms in the present study and in a previous study (16) may be explained by the hypothesis that norepinephrine derived from brain regions which are not directly related to schizophrenic psychopathology contributes significantly to the total CSF pool, resulting in the failure of CSF levels to correlate with psychopathology. In addition, van Kammen et al. (12) reported that CSF norepinephrine significantly relates to schizophrenic symptoms in relapsing schizophrenic patients but not in nonrelapsing schizophrenic patients, suggesting the sample differences may also explain lack of correlation between CSF norepinephrine levels and symptoms in the present study.

Data from the present report and previous studies support the notion that altered peripheral sympathoneural activity may represent altered CNS processes. We found that CNS norepinephrine was significantly related to plasma norepinephrine, which is consistent with previous findings of significant correlations between CSF and plasma norepinephrine levels (26, 27). In addition, we found that CSF HVA levels were negatively correlated with resting, standing, and change in plasma norepinephrine levels. A large body of data indicate that there is a dynamic relationship between dopaminergic and noradrenergic function, which may be either inhibitory or facilitative depending on the compensatory needs of the organism (46, 47). Thus, it is possible that the above-normal peripheral sympathetic nervous system activity found in this and other studies of schizophrenia reflects altered central processes involving dopaminergic and noradrenergic function. This hypothesis is supported by our recent study demonstrating simultaneous alterations in noradrenergic and dopaminergic activity in chronic schizophrenic patients (16).

In conclusion, the findings from the present study contribute to a growing body of data from post-mortem (1–5), CSF (6–12, 16), plasma (13–16), and pharmacologic (17–19) studies that indicate altered noradrenergic function in schizophrenia. It will be important for future studies to elucidate the mechanisms that contribute to altered noradrenergic function in schizophrenia and to determine the significance of these findings for the etiology and treatment of this illness.

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Influence of Patient-Related Variables on Clozapine Plasma Levels

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The authors investigated the clozapine plasma levels of 148 psychiatric inpatients. Multiple regression analysis revealed a linear relationship between dose of clozapine and plasma concentrations. The analysis showed a significant influence of dose, sex, smoking, weight, and age on the plasma concentrations of clozapine under clinical conditions. These results remained significant when clozapine doses below 150 mg/day and above 500 mg/day were excluded from the analysis.

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The determination of plasma levels for clinical applications is highly desirable to reveal compliance problems in patients, to keep drug exposure to the minimum necessary, and to deal with medicolegal problems (1). There are great interindividual differences in the plasma levels of many drugs used in psychiatry. Different patients treated with chlorpromazine, for example, may have serum drug levels that vary by 100% (2).

Clozapine is a neuroleptic drug that is increasingly used in the management of psychiatric inpatients and outpatients. The special feature of this drug is a lack of extrapyramidal motor side effects, which makes it stand out from the conventional high-potency neuroleptics (3). To gain more information on plasma levels of clozapine under clinical conditions, we evaluated the routinely monitored plasma concentrations of clozapine at our inpatient facility. This report deals with the effect of dose, age, weight, sex, and smoking behavior on the plasma levels of clozapine.

METHOD

Plasma levels of clozapine were measured in 148 psychiatric inpatients (54 women and 94 men) with a mean±SD age of 30.6±8.8 years who were receiving clozapine for acute or maintenance treatment. Seventeen (31.5%) of the women and 14 (14.9%) of the men suffered from manic episodes (diagnosed according to *DSM-III*), 37 (68.5%) of the women and 80 (85.1%) of the men had schizophrenia (*DSM-III*). Sixty-seven patients were nonsmokers and 81 patients smoked more than five cigarettes a day.

Clozapine was given orally in a daily dose that was kept constant for at least 8 days. The individual doses for these patients ranged from 12.5 to 700 mg/day (mean=281±141 mg/day) depending on clinical demands. Blood samples were taken in the morning before breakfast, 10±1 hours after administration of the last dose of clozapine.

Plasma levels were determined by reversed-phase, high-performance liquid chromatography and ultraviolet detection as described in detail elsewhere (4). All reagents were standard laboratory reagents of analytical grade.

Analysis of variance (ANOVA), regression analysis, and multiple regression analysis were applied where appropriate. Since plasma levels and patients' ages were not normally distributed, a logarithmic transformation of these variables was necessary. A second analysis was performed in which only patients who were given doses within the range of 150–500 mg/day were included. This was done to correct for the statistical problems caused by extreme outliers at the lower and upper extremes of dose and plasma levels. ANOVAs were carried out by using Bio-Medical Data Programs; SPSS forward stepping was used for multiple regression analyses.

RESULTS

Various interactions among the analytical variables were apparent when patients were compared by using ANOVA (see tables 1 and 2). To account for these differences, further analyses were carried out by using multiple regression. Table 1 provides the data for the

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TABLE 1. Characteristics of 148 Psychiatric Inpatients Given 12.5–700 mg/day of Clozapine

Variable	All Patients (N=148)	Men (N=94)	Women (N=54)	Smokers (N=81)	Nonsmokers (N=67)	Younger Than 30.5 Years Old (N=74)	30.5 Years Old or Older (N=74)
Age[a]							
Mean	30.6	28.9	33.5	29.8	31.5	25.0	39.3
SD	8.8	7.8	9.8	7.2	10.5	3.1	6.6
Median	30.5	29.0	33.0	32.0	30.0	—	—
Range	18.5–53.5	18.5–50.5	19.5–53.5	19.5–45.5	18.5–53.5	20.0–30.0	31.0–55.0
Weight (kg)[b]							
Mean	74.8	77.6	69.9	75.1	74.4	71.9	76.5
SD	15.2	15.9	12.6	16.5	13.5	12.4	12.6
Range	50.0–176.0	50.0–176.0	50.0–98.0	50.0–176.0	50.0–100.0	50.0–95.0	50.0–100.0
Medication dose (mg/day)[c]							
Mean	280.0	303.6	241.7	262.0	303.9	285.8	276.2
SD	141.0	141.8	131.8	131.5	149.6	154.9	126.5
Range	12.0–700.0	12.0–700.0	25.0–600.0	25.0–700.0	12.0–700.0	25.0–700.0	12.0–700.0
Plasma level (ng/ml)[d]							
Mean	160.1	149.5	178.6	141.0	183.2	155.7	164.5
SD	121.5	116.7	128.6	114.2	15.5	114.3	129.0
Range	9.7–529.7	9.7–529.7	10.0–486.0	9.7–469.2	10.2–529.7	9.7–529.7	10.2–493.1

[a] There was a significant difference (one-way ANOVA) between men and women (F=11.08, df=1, 146, p=0.001) and between patients younger than 30.5 and those 30.5 years old and older (F=281.83, df=1, 146, p=0.000).

[b] There was a significant difference (one-way ANOVA) between men and women (F=10.33, df=1, 146, p=0.002) and between patients younger than 30.5 and those 30.5 years old and older (F=5.08, df=1, 146, p=0.03).

[c] There was a significant difference (one-way ANOVA) between men and women (F=6.88, df=1, 146, p=0.01).

[d] There was a significant difference (one-way ANOVA) between smokers and nonsmokers (F=5.80, df=1, 146, p=0.02).

TABLE 2. Characteristics of 122 Psychiatric Inpatients Given 150–500 mg/day of Clozapine

Variable	All Patients (N=122)	Men (N=81)	Women (N=41)	Smokers (N=66)	Nonsmokers (N=56)	Younger Than 30.5 Years Old (N=60)	30.5 Years Old or Older (N=62)
Age[a]							
Mean	32.8	30.7	36.9	32.1	33.5	25.4	39.9
SD	9.0	8.0	9.6	7.3	10.7	3.6	6.6
Median	33.0	29.0	33.0	33.0	31.0	—	—
Range	20.0–55.0	20.0–52.0	21.0–55.0	21.0–47.0	20.0–55.0	20.0–32.0	33.0–55.0
Weight (kg)[b]							
Mean	74.7	76.7	70.7	75.0	74.3	71.4	77.8
SD	12.9	12.1	13.6	12.5	13.4	12.4	12.6
Range	50.0–100.0	50.0–100.0	50.0–98.0	50.0–98.0	50.0–100.0	50.0–95.0	50.0–100.0
Medication dose (mg/day)							
Mean	288.1	292.3	279.9	276.5	301.8	290.8	285.5
SD	99.8	99.4	101.1	94.6	104.8	99.3	101.0
Range	150.0–500.0	150.0–500.0	150.0–500.0	150.0–500.0	150.0–500.0	150.0–500.0	150.0–500.0
Plasma level (ng/ml)[c]							
Mean	162.2	141.0	204.0	149.2	177.4	149.4	174.5
SD	110.9	98.0	123.6	110.6	110.3	84.1	131.2
Range	9.7–493.1	9.7–493.1	47.0–486.0	9.7–469.2	12.3–493.1	9.7–361.1	10.3–493.1

[a] There was a significant difference (one-way ANOVA) between men and women (F=14.27, df=1, 120, p=0.000) and between patients younger than 30.5 and those 30.5 years old and older (F=225.85, df=1, 120, p=0.000).

[b] There was a significant difference (one-way ANOVA) between men and women (F=6.20, df=1, 120, p=0.01) and between patients younger than 30.5 and those 30.5 years old and older (F=7.93, df=1, 120, p=0.006).

[c] There was a significant difference (one-way ANOVA) between men and women (F=9.39, df=1, 120, p=0.003).

TABLE 3. Multiple Regression of Effect on Clozapine Plasma Levels of Other Variables in 148 Psychiatric Inpatients

	Dose Range=12.5–700 mg/day			Dose Range=150–500 mg/day		
Item	Total (N=148)	Men (N=94)	Women (N=54)	Total (N=122)	Men (N=81)	Women (N=41)
Multiple R	0.61	0.64	0.75	0.46	0.52	0.63
R^2	0.37	0.41	0.56	0.21	0.28	0.39
Adjusted R^2	0.36	0.39	0.53	0.20	0.25	0.34
Standard error	0.31	91.33	88.22	0.31	0.31	0.23
ANOVA						
F	20.09	20.62	20.86	16.21	9.73	7.99
df	3, 144	3, 90	3, 50	2, 119	3, 77	3, 37
p	0.000	0.000	0.000	0.000	0.000	0.000
Independent variables in the equation						
Dose (step 1)						
Simple R (dose/plasma level)	0.55[a]	0.59[a]	0.60[a]	0.36	0.38	0.43[a]
Sex (step 2)						
Multiple R	0.59			0.46		
Simple R (sex/plasma level)	0.12			0.27[b]		
Weight (steps 2 and 3)						
Multiple R		0.64	0.69		0.47	0.63
Simple R (weight/plasma level)		−0.17	0.38[b]		−0.29[b]	0.40[c]
Smoking behavior (steps 2 and 3)						
Multiple R	0.61	0.62			0.52	
Simple R (smoking behavior/plasma level)	−0.17[a]	−0.27[b]			−0.22	
Age (steps 2 and 3)						
Multiple R			0.75			0.56
Simple R (age/plasma level)			0.45[a]			0.40[c]
Simple R						
Dose/sex	−0.21[b]			−0.06		
Dose/smoking behavior	−0.15	−0.18			−0.16	
Dose/weight		−0.07	0.09		−0.16	0.01
Dose/age			0.24			
Sex/smoking behavior	0.10					
Weight/smoking behavior		−0.19			−0.15	0.01
Weight/age			0.10			0.12

[a] $p<0.001$.
[b] $p<0.01$.
[c] $p<0.05$.

analysis of patients given clozapine doses in the entire range of 12.5–700 mg/day, and table 2 provides the data for the patients given 150–500 mg/day.

When different doses of clozapine were compared with the corresponding plasma levels, regression analysis revealed a linear relationship between dose and plasma level (see table 3). Since very high and very low doses can influence this regression, a second analysis was performed in which only patients given a dose range of 150–500 mg/day, corresponding to the second and third quartile of the whole sample, were included. Regression analysis also revealed that sex had an important influence on plasma levels; therefore, the data on patients given the full dose range and those given the more narrow dose range were calculated separately for each sex.

Regression analysis of the plasma levels from all patients demonstrated that medication dose, sex, smoking behavior, weight, and age explained 36.9% of the whole variance (see table 3). The analysis of patients given the narrower dose range of 150–500 mg/day showed that the results were influenced by extreme outliers at the lower and upper dose extremes. When patients given such extreme doses were excluded, the percentage of explained variance dropped to 21.4%, which is still statistically significant.

Dose had the biggest influence on all subgroups of patients. In men, smoking behavior ranked second in influence for the patients given the full dose range and third in influence for those given the more narrow dose range. In women, weight ranked second in influence for those given the wider dose range and age ranked second for those given the lower dose range. Smoking behavior was not significantly associated with plasma level in women.

There were no significant correlations among dose, sex, smoking behavior, and age except between dose and sex for patients given the full dose range of clozapine. This can be seen as an indicator for the independence of the analytical predictors relating to the dependent variable, plasma level.

DISCUSSION

Only a few reports have dealt with the issue of correlations between clozapine dose and plasma levels. Ackenheil et al. (5) used gas chromatography (N=19) or radioimmunoassay (N=7) to detect clozapine plasma levels in 26 patients. They found a linear correlation (r=0.65) between dose and plasma concentration after 10 days of treatment with clozapine doses ranging from 100 to 600 mg/day, which is very similar to our results. Although Ackenheil et al. corrected their results for body weight, they provided no information as to whether the dose had been held at a constant level for the days preceding the plasma level analysis. Neither age nor sex had an influence on these results. This apparent difference from our results might be attributed to the considerably lower number of patients in their study. Another methodological problem in the paper by Ackenheil et al., which they acknowledged themselves, is that they used two different analytical procedures for the evaluation of the plasma levels.

The issue of correlations between dose and plasma levels was also addressed in a case report by Kane et al. (6) that focused on clozapine plasma levels and prolactin response. Since the authors reported data on only two patients, they did not provide a statistical analysis, but it appears from the graphs in their paper that clozapine plasma levels corresponded to the doses administered.

Our results demonstrate a correlation between clozapine plasma concentrations and a given oral dose. This held up in two analyses. These findings are similar to the results reported by Hippius and Ackenheil (7) and Heipertz et al. (8). Breyer et al. (9) found high interindividual variations in patients treated with similar doses of clozapine.

We obtained a marked difference in clozapine plasma levels between men and women. This has also been reported for other psychotropic drugs—benzodiazepines, for example (10).

Plasma concentrations at a given dose were found to be lower in smokers than in nonsmokers. Similar results have been reported by Ereshefsky et al. (11) for fluphenazine and are known for many other drugs (theophylline, phenacetin, and propranolol, for example [12–14]). This may be the result of changes in enzyme activity in the liver and/or the gastrointestinal tract caused by nicotine and/or other substances incorporated by smoking (15). The fact that smoking had a significant effect on plasma levels in men but not in women can possibly be explained by a sex difference in smoking behavior. We defined a smoker as a person who smokes more than five cigarettes a day with no upper limit. This means that the women who were classified as smokers might have smoked fewer cigarettes than the men who were so classified, which would reduce cigarette-induced alterations of plasma levels in the women.

The significant influence of age on clozapine plasma levels may be a result of the decreasing liver enzyme activity in older people. This phenomenon is well described for other psychotropic agents (16). Klein et al. (17) found no dependence between patients' age and plasma levels in a group of 32 patients. The difference between their findings and ours might be attributed to the considerably lower number of patients in their study.

The clozapine plasma levels varied widely among individual patients. This is also true for other neuroleptics and may be one of the reasons that it has not been possible to establish a well-defined relationship between plasma level and response. Further investigations are necessary to clarify whether this is the result of altered kinetics and/or metabolism or a compliance problem. It will be interesting to see whether a therapeutic range can be found for clozapine, as has been proposed for haloperidol, and how plasma levels relate to side effects of the drug. Ackenheil et al. (5) also attempted to answer the latter question and found no significant correlation between sedation or orthostatic hypotension and clozapine plasma levels.

The present results indicate a considerable variation in clozapine plasma levels at a given dose depending on a number of factors. These factors should be taken into consideration for efficient therapy with the lowest possible dose.

Because of the retrospective, naturalistic design of this study, the principal metabolites of clozapine, the corresponding N-oxide and N-desmethyl derivatives, were not measured.

Even though the results described here are based on a naturalistic study that did not follow the strict criteria of a controlled prospective design, we still think they have clinical relevance. The fact that all patients were in a clinical setting seems to warrant the conclusion that the differences in plasma levels between different sexes and age groups as well as between smokers and nonsmokers might influence the therapeutic efficacy of clozapine in these patients. This assumption is of course made under the presupposition that there is a relation between plasma levels and therapeutic efficacy.

It has to be emphasized that the variables investigated account for only a small, but statistically significant, explanation of the variance. This clearly calls for further prospective studies looking at other potential influences on correlations between dose and plasma levels, such as duration of intake or diagnosis.

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Personality Differences Between Patients With Remitted Melancholic and Nonmelancholic Depression

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Seventy-five patients with remitted depression were categorized as having melancholic-endogenous or nonmelancholic-nonendogenous depression according to DSM-III *criteria, Research Diagnostic Criteria, and the Newcastle endogeneity scale. The patients' scores on four personality scales—the Eysenck Personality Inventory, the Interpersonal Dependency Inventory, locus of control, and the Interpersonal Sensitivity Measure—were then compared. Patients with nonmelancholic-nonendogenous depression were generally rated as having more vulnerable personality styles, but the differences were dependent on the particular diagnostic system used. A principal components analysis isolated three underlying personality constructs—dependency, introversion, and timidity. Patients with nonmelancholic-nonendogenous depression scored as significantly more dependent.*

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The heterogeneous nature of depression and the differing etiologies and symptom patterns ascribed to different subtypes suggest the variable relevance of possible predisposing personality factors (1). Although types of depression may be contrasted in a number of ways (unipolar versus bipolar, primary versus secondary, and melancholic versus nonmelancholic), the differential relevance of personality factors has emerged most clearly in relation to the melancholic versus nonmelancholic system, which is based on the binary view of depression.

The binary view holds that one type of depression (variably termed "endogenous" or "melancholic") is a categorical entity with "an imputed genetic or biochemical basis" (2) and without any predisposing personality style. Many different definitions have been proposed for patients with nonendogenous-nonmelancholic depression, who are often thought to have vulnerable personality styles (3). For instance, in a number of factor-analytic studies, vulnerable personality characteristics have either loaded on the neurotic pole of an endogenous-neurotic factor (2, 4) or correlated with a clinical diagnosis of neurotic depression (5). By contrast, characteristics of an adequate personality have correlated with a diagnosis of endogenous depression (6). A limitation to the studies cited is that both personality variables and clinical diagnoses were generated by the clinician, so that a judgment of vulnerable personality may have encouraged a confirming diagnosis of neurotic depression and the converse bias for patients with endogenous depression.

More formalized evaluations of personality traits using personality questionnaires have been undertaken, but clear and consistent differences have not been demonstrated between types of depression. Quite reasonably, assessment has focused on depression-prone personality characteristics such as neuroticism (7), obsessionality (8), and dependency (9, 10).

Neuroticism and extraversion, as defined by Eysenck (11), have been the most commonly assessed constructs. Patients with endogenous depression have been found to have lower neuroticism (12–14) and higher extraversion (12) levels in some studies, although in other studies (15–17) neuroticism and extraversion have failed to discriminate between types of depression. Additionally, one study (18) reported higher levels of neuroticism (and other measures of low emotional strength) in a group of patients with "nuclear" depression (consisting of "a nucleus of patients common to multiple definitions of endogenous depression," identified by means of latent class analysis).

Obsessional traits have been reported to be associated with "agitated depression" (19), "involutional melancholia" (20, 21), and bipolar depression (8). Obsessional symptoms, particularly ruminations (22, 23), are more common in endogenous depression. One contrary study (24) reported that patients with different types of depression did not differ in scores on the Leyton obsessionality scale.

Dependency is a personality trait often implicated as a risk factor in depression (9, 10). Although higher

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levels of dependency and submissiveness have been reported in patients with endogenous depression compared with patients with nonendogenous depression (14, 25) and in patients with nuclear depression compared with those with nonnuclear depression (18), one study (26) reported higher levels of dependency in patients with nonendogenous depression.

These inconsistent results may reflect methodological limitations. Since depressive mood has the potential to distort (usually inflating) scores on personality measures, an abnormal premorbid personality style might be suggested erroneously if personality is assessed while the subject is depressed (27). Again, the use of different and not necessarily equivalent diagnostic criteria for contrasting types of depression may obscure differences. For example, Zimmerman et al. (28) have shown that the rates of personality disorders (and other risk factors) differ according to whether *DSM-III* or *DSM-III-R* criteria for melancholia are applied to the same patient group.

In this study we seek to overcome these methodological difficulties in examining the hypothesis that patients with nonmelancholic depression are more likely than patients with melancholic depression to have vulnerable personality characteristics. Any bias emerging from the patient's depressive state distorting personality scores on self-report measures may be overcome in two broad ways. First, a prospective study design can be used: subjects are assessed before any episode of depression to measure true vulnerability. Such a design is impractical because a very large sample size is needed to overcome the low base rate of melancholic depression and because nonpersonality variables (such as depressogenic stressors) cannot be standardized readily. The alternative but not ideal approach (because there may be residual personality anomalies) is to assess subjects when their depressive episodes have remitted. We used the latter approach in this study. To overcome limitations associated with any one diagnostic system used to subtype depressive disorders, we examined several diagnostic systems. Finally, we restricted personality scales to those suggested as identifying depression-prone personality characteristics.

METHOD

The subjects for this study were a subgroup of the first 250 inpatients and outpatients assessed at a university hospital mood disorders unit, a facility somewhat weighted to patients with chronic and/or treatment-resistant disorders. At baseline, all patients were assessed by using a semistructured interview (29), allowing the clinician to make typological decisions by using *DSM-III*, Research Diagnostic Criteria (RDC) (30), and the Newcastle endogeneity scale (6). The severity of depression was assessed by using the clinician-rated Hamilton Rating Scale for Depression (31) and the Zung Self-Rating Depression Scale (32). Twenty weeks after baseline assessment, patients were seen again, depression scales were readministered, and a clinical judgment was made about remission. Patients were judged to be in remission if they no longer met criteria for major depression and were no longer impaired by depression despite any residual symptoms.

Subjects included in the study were required to be in remission at the 20-week assessment, to have completed all personality measures at this assessment, and to have been nonpsychotic at the baseline assessment (to exclude those whose capacity to give valid information might have been reduced).

Personality Measures

Subjects completed the following personality measures at baseline and at 20 weeks: the extraversion and neuroticism subscales of the Eysenck Personality Inventory (11), the Interpersonal Dependency Inventory (33), a locus of control measure (34), and the Interpersonal Sensitivity Measure (35). The Interpersonal Sensitivity Measure is a 36-item, self-report scale. Each item is scored on a 4-point Likert scale, allowing total scores on the instrument to range from 36 to 144. The scale measures five components of interpersonal sensitivity: 1) interpersonal awareness, referring to the way an individual appraises and accords meaning to a situation, 2) need for approval, assessing the extent to which an individual needs to be approved of by others, 3) separation anxiety, assessing any undue anxiety about possible separation from a significant other, 4) timidity, focusing on behavioral aspects of depression-prone characteristics, particularly the inability to behave assertively, and 5) fragile inner self, which identifies difficulty with self-disclosure for fear of being rejected or ridiculed. The Interpersonal Sensitivity Measure has satisfactory internal consistency (Cronbach's alpha=0.85), was stable over time in a nonclinical group (test-retest coefficient=0.70), but, like the Eysenck Personality Inventory and the Interpersonal Dependency Inventory, shows some sensitivity to depressed mood (36).

The patients were asked to rate themselves generally, not as they might necessarily be feeling at the time of assessment, as suggested by Kendell and DiScipio (37).

Data Analysis

Because the aim of this study was to determine differences between patients with melancholic-endogenous and nonmelancholic-nonendogenous depression, patients were divided into *DSM-III* melancholic and nonmelancholic (major depression and dysthymia) types, RDC endogenous (definite) and nonendogenous (probable endogenous, definite major depression, and intermittent depression), and Newcastle endogenous (a score of 6 or more on the Newcastle scale) and nonendogenous.

First, we examined for differences between the patients with different types of depression on the personality measures using analyses of variance; age and se-

TABLE 1. Age and Severity of Depression in Patients With Different Types of Depression According to Three Diagnostic Systems

Diagnostic System and Type of Depression	Age[a] (years)		Severity of Depression at Baseline				Severity of Depression at 20 Weeks			
			Hamilton Scale[b]		Zung Scale		Hamilton Scale[c]		Zung Scale[d]	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
DSM-III										
Melancholic subtype (N=27)	54.2	16.1	18.5	7.1	49.5	10.3	4.9	4.0	36.4	10.9
Nonmelancholic subtype (N=48)	42.2	15.3	14.5	7.5	51.6	9.9	6.8	5.6	43.1	12.6
Newcastle criteria										
Endogenous type (N=15)	55.3	16.9	17.4	6.3	49.4	12.5	3.4	3.5	34.1	11.2
Nonendogenous type (N=60)	44.4	15.9	15.6	7.9	51.3	9.5	6.8	5.3	42.4	12.2
RDC										
Endogenous type (N=36)	52.2	16.9	19.2	7.6	51.1	9.7	5.5	4.1	37.9	10.8
Nonendogenous type (N=39)	41.3	14.6	13.0	6.4	50.7	10.4	6.7	5.9	43.3	13.3

[a] The differences between patients with *DSM-III* melancholic and nonmelancholic depression (F=10.12, df=1, 74, $p<0.05$) and between patients with RDC endogenous and nonendogenous depression (F=8.97, df=1, 74, $p<0.01$) were significant.

[b] The differences between patients with *DSM-III* melancholic and nonmelancholic depression (F=5.0, df=1, 74, $p<0.05$) and between patients with RDC endogenous and nonendogenous depression (F=13.83, df=1, 74, $p<0.001$) were significant.

[c] The difference between patients with endogenous and nonendogenous depression according to Newcastle criteria was significant (F=5.03, df=1, 74, $p<0.05$).

[d] The differences between patients with *DSM-III* melancholic and nonmelancholic depression (F=5.22, df=1, 74, $p<0.05$) and between patients with endogenous and nonendogenous depression according to Newcastle criteria (F=5.33, df=1, 74, $p<0.05$) were significant.

TABLE 2. Scores on Personality Measures of Patients With *DSM-III* Melancholic or Nonmelancholic Depression

Personality Measure	Patients With Melancholic Subtype (N=27)		Patients With Nonmelancholic Subtype (N=48)		F		
	Mean	SD	Mean	SD	Overall (df=1, 73)	Age Controlled for (df=1, 72)	Severity of Depression[a] Controlled for (df=1, 72)
Eysenck Personality Inventory							
Neuroticism	12.1	6.1	13.9	5.0	1.95	0.56	1.02
Extraversion	9.6	4.6	9.0	4.5	0.38	0.36	0.06
Interpersonal Dependency Inventory							
Assertion of autonomy	26.6	5.7	27.1	7.4	0.40	0.38	1.84
Lack of social self-confidence	33.1	9.6	37.2	9.3	4.13	2.28	1.94
Emotional reliance on another	39.6	11.0	44.1	10.4	3.37	2.85	2.21
Interpersonal Sensitivity Measure							
Interpersonal awareness	18.4	5.0	21.5	4.1	8.67[b]	6.22	6.24
Need for approval	25.0	3.3	25.8	3.6	0.88	1.85	5.50
Separation anxiety	16.8	5.4	20.9	5.2	10.19[b]	6.44	7.52[b]
Timidity	21.6	4.7	23.2	4.5	2.33	3.33	1.03
Fragile inner self	9.9	3.9	12.5	3.3	9.64[b]	4.63	7.33[b]
Total	91.7	17.9	104.0	15.7	9.64[b]	7.33[b]	6.94
Locus of control	28.1	11.8	34.5	11.3	5.35[b]	3.25	3.95

[a] Based on Hamilton depression scale score.

[b] Bonferroni $p<0.05$.

verity of depression were controlled for in analyses of covariance. To minimize the chance of a type I error, each personality scale was considered to be a family of tests (38). A Bonferroni adjustment was carried out for each personality scale. Thus, for the Interpersonal Sensitivity Measure, $\alpha=0.008$, for the Interpersonal Dependency Inventory, $\alpha=0.02$, and for the Eysenck Personality Inventory, $\alpha=0.025$. Second, although separate

TABLE 3. Scores on Personality Measures of Patients With Endogenous or Nonendogenous Depression According to Newcastle Criteria

Personality Measure	Patients With Endogenous Depression (N=15)		Patients With Nonendogenous Depression (N=60)		F		
	Mean	SD	Mean	SD	Overall (df=1, 73)	Age Controlled for (df=1, 72)	Severity of Depression[a] Controlled for (df=1, 72)
Eysenck Personality Inventory							
Neuroticism	10.0	6.4	14.1	4.9	7.14[b]	4.92	4.77
Extraversion	10.1	5.2	9.0	4.3	0.80	0.78	0.16
Interpersonal Dependency Inventory							
Assertion of autonomy	26.2	5.5	27.1	7.2	0.88	0.46	0.09
Lack of social self-confidence	29.5	7.7	37.3	9.4	11.01[c]	7.43[b]	5.81[b]
Emotional reliance on another	37.5	10.5	43.7	10.5	4.81	3.91	2.91
Interpersonal Sensitivity Measure							
Interpersonal awareness	16.3	3.9	21.4	4.3	17.91[d]	15.03[d]	13.11[c]
Need for approval	24.5	3.5	25.8	3.5	1.45	2.31	0.91
Separation anxiety	15.0	4.3	20.6	5.3	13.93[c]	10.44[b]	9.52[b]
Timidity	21.6	2.7	22.9	4.9	0.93	1.30	0.05
Fragile inner self	8.9	3.7	12.3	16.7	10.59[b]	6.55	10.27[b]
Total	86.3	13.8	102.8	16.7	12.46[b]	10.27[b]	8.08[b]
Locus of control	27.3	11.9	33.5	11.6	2.21	3.25	1.90

[a] Based on Hamilton depression scale score.
[b] Bonferroni $p<0.05$.
[c] Bonferroni $p<0.01$.
[d] Bonferroni $p<0.001$.

personality scales were administered, several appeared to address similar personality constructs, suggesting that a refined analysis might be useful in defining personality styles at risk for depression. To this end, we undertook a principal components analysis (with oblique rotation), deriving factor scores for each of the subjects, and examined for differences on these refined personality constructs using t tests.

RESULTS

Seventy-five patients met the criteria for the study; their mean±SD age was 43.5±16.6 years. At baseline assessment, the subjects had a mean Hamilton score of 15.9±7.6 and a mean Zung score of 51.2±10.0, and at the 20-week assessment their mean Hamilton score had decreased significantly to 6.1±5.1 ($t=9.06$, $df=1, 71$, $p<0.001$) and the mean Zung score to 40.8±12.4 ($t=5.97$, $df=1, 69$, $p<0.001$). Twenty-one (28%) of the subjects were male. Twenty-seven (36%) of the patients had *DSM-III* melancholia, 36 (48%) of the patients had RDC definite endogenous depression, and 15 (20%) of the patients fulfilled the Newcastle criteria for endogenous depression.

The highest level of agreement across diagnostic systems was between *DSM-III* melancholia and RDC endogenous depression (kappa=0.70), followed by *DSM-III* melancholia with Newcastle endogenous depression (kappa=0.56), but there was poor agreement between RDC (the most "liberal" diagnostic system) and Newcastle (the most restrictive system) endogenous depression (kappa=0.37). For each diagnostic system, the patients with endogenous depression were older and scored higher on the Hamilton depression scale at the baseline assessment (significantly for the *DSM-III* and RDC systems) but not on the Zung scale (see table 1). At the 20-week assessment the patients with melancholic-endogenous depression scored as less depressed on the Hamilton and Zung rating scales (see table 1).

Patients with *DSM-III* nonmelancholic depression tended to have scores indicating more deviance on the personality measures than did those with melancholic depression, as shown in table 2. The only differences that remained significant after the severity of depression was controlled for, however, were for the separation anxiety and fragile inner self subscales of the Interpersonal Sensitivity Measure. The total Interpersonal Sensitivity Measure score was significant after age, but not severity, was controlled for.

Patients with nonendogenous depression as defined by the Newcastle system also tended to have scores indicating more deviance on the personality measures than did those with endogenous depression (see table 3). Their scores on the Interpersonal Dependency Inventory lack of social self-confidence subscale and on the Interpersonal Sensitivity Measure interpersonal

TABLE 4. Scores on Personality Measures of Patients With Endogenous or Nonendogenous Depression According to the RDC

	Patients With Endogenous Depression (N=36)		Patients With Nonendogenous Depression (N=39)		F		
Personality Measure	Mean	SD	Mean	SD	Overall (df=1, 73)	Age Controlled for (df=1, 72)	Severity of Depression[a] Controlled for (df=1, 72)
Eysenck Personality Inventory							
Neuroticism	13.4	5.8	13.1	5.2	0.67	1.00	0.30
Extraversion	9.7	4.6	8.8	4.4	0.74	0.73	0.41
Interpersonal Dependency Inventory							
Assertion of autonomy	25.9	6.4	27.9	7.1	2.34	2.63	1.44
Lack of social self-confidence	35.2	10.1	36.2	9.2	0.45	0.01	0.02
Emotional reliance on another	41.7	11.0	43.2	10.7	0.44	0.21	0.17
Interpersonal Sensitivity Measure							
Interpersonal awareness	19.4	5.0	21.3	4.2	3.44	1.92	2.53
Need for approval	25.4	3.2	25.6	3.8	0.04	0.31	0.01
Separation anxiety	18.1	5.4	20.7	5.6	4.09	1.85	3.10
Timidity	22.0	4.6	23.2	4.6	1.41	2.07	0.78
Fragile inner self	10.4	3.8	12.7	3.4	7.69[b]	3.46	6.57
Total	95.3	17.8	103.5	16.3	4.40	2.83	3.37
Locus of control	30.1	11.4	34.2	12.1	2.22	2.17	1.67

[a] Based on Hamilton depression scale score.
[b] Bonferroni $p<0.05$.

awareness subscale, separation anxiety subscale, and total remained significantly higher than did those of patients with endogenous depression after age and severity had been controlled for (see table 3).

When the RDC was used as the diagnostic system, no significant differences were found between the groups (see table 4).

Although the clearest differences between diagnostic types were found with the Newcastle criteria, there is circularity in this finding because the Newcastle scale includes adequate personality as a criterion. Patients with an adequate personality would, by definition, be more likely to be judged as having endogenous depression. To overcome this bias, the adequate personality item was deleted and the cutoff for endogenous depression on the Newcastle scale was reduced from 6 to 5. With this new cutoff, 18 (24%) of the patients were then categorized as having endogenous depression. Compared with the 57 patients then categorized as having nonendogenous depression, these 18 patients had a lower neuroticism score (10.3±6.5 versus 14.2±4.8, F=7.28, df=1, 73, $p<0.01$) on the Eysenck Personality Inventory and a lower total score (88.8±15.2 versus 102.9±16.8, F=10.05, df=1, 73, $p<0.05$), lower interpersonal awareness score (17.2±4.5 versus 21.4±4.3, F=13.08, df=1, 73, $p<0.01$), lower separation anxiety score (16.0±4.9 versus 20.5±5.4, F=10.10, df=1, 73, $p<0.05$), and lower fragile inner self score (9.3±3.5 versus 12.3±3.6, F=9.52, df=1, 73, $p<0.05$) on the Interpersonal Sensitivity Measure. They also scored lower on the Interpersonal Dependency Inventory subscales of lack of social self-confidence (28.5±10.0 versus 37.6±9.4, F=12.54, df=1, 73, $p<0.01$) and emotional reliance on another (37.4±10.5 versus 43.9±10.7, F=4.99, df=1, 73, n.s.) and on the locus of control measure (27.4±10.9 versus 33.8±11.8, F=4.15, df=1, 73, $p<0.05$).

The principal components analysis including all personality measures generated three factors with an eigenvalue greater than 1 and accounted for 69.6% of the total variance; the first factor accounted for 44.6% of the total variance. Factor loadings for the three rotated factors are shown in table 5. The first factor suggests a dependency dimension; two of the Interpersonal Dependency Inventory subscales (emotional reliance on another and lack of social self-confidence) as well as three of the Interpersonal Sensitivity Measure subscales (separation anxiety, interpersonal awareness, and fragile inner self) loaded on this factor. Neuroticism and external locus of control also loaded on this factor. Patients with *DSM-III* melancholic depression scored significantly lower on this factor than did patients with nonmelancholic depression (−0.42 versus 0.23, t=2.85, df=73, $p<0.01$), as did patients with endogenous depression diagnosed by the Newcastle criteria (−0.80 versus 0.20, t=3.77, df=73, $p<0.001$). Although patients with endogenous depression diagnosed by the RDC scored lower than patients with nonendogenous depression (−0.16 versus 0.15), the difference was not statistically significant.

The second factor isolated an introversion dimension; loadings from the Eysenck Personality Inventory

TABLE 5. Factor Loadings for Three Factors Isolated by Principal Components Analysis

Psychological Measure	Factor 1: Dependency	Factor 2: Introversion	Factor 3: Timidity
Interpersonal Dependency Inventory: emotional reliance on another	0.86	−0.21	0.08
Eysenck Personality Inventory: neuroticism	0.83	−0.16	0.04
Interpersonal Dependency Inventory: lack of social self-confidence	0.80	0.27	0.03
Locus of control	0.75	0.12	0.10
Interpersonal Sensitivity Measure: separation anxiety	0.71	0.06	−0.35
Interpersonal Sensitivity Measure: interpersonal awareness	0.62	0.01	−0.42
Interpersonal Sensitivity Measure: fragile inner self	0.58	0.20	−0.31
Eysenck Personality Inventory: extraversion	0.00	−0.83	0.24
Interpersonal Dependency Inventory: assertion of autonomy	0.07	0.72	0.24
Interpersonal Sensitivity Measure: timidity	0.00	0.10	−0.88
Interpersonal Sensitivity Measure: need for approval	0.12	−0.44	−0.60

extraversion scale (loading negatively) and the assertion of autonomy subscale of the Interpersonal Dependency Inventory (loading positively) were most distinct. The items on the assertion of autonomy subscale identify a preference for being alone rather than necessarily referring to being autonomous or independent, which explains the negative correlation between these two scales. No differences were found between the diagnostic groups on the factor scores derived from this scale, although there was a trend for the patients with endogenous depression to score lower on this factor, suggesting that patients with nonendogenous depression were more introverted.

The third factor isolated two aspects of interpersonal sensitivity—timidity and a need for approval. No differences were found between the diagnostic groups on this factor.

DISCUSSION

The results reported here give some support to the proposition that patients with melancholic-endogenous depression have scores indicating less deviance than patients with nonmelancholic-nonendogenous depression on personality measures held to reflect risk factors for depression. However, although the patients with endogenous depression had scores indicating less deviance on the personality measures, only a few of the differences were statistically significant (particularly after age and severity were partialed out), perhaps a result of our setting alpha conservatively to minimize a type I error. The most pronounced differences between diagnostic types were found for patients diagnosed according to the Newcastle scale—patients with endogenous depression showed less interpersonal sensitivity, less emotional reliance on another, and lower neuroticism than did patients with nonendogenous depression. Differences were also established for the patients with *DSM-III* melancholic depression, who, in addition, had lower interpersonal sensitivity and dependency scores than the patients with nonendogenous depression. When the Newcastle scale was modified to remove the adequate personality item and the cutoff score was lowered, the differences for neuroticism, Interpersonal Sensitivity Measure subscales, and the lack of social self-confidence subscale of the Interpersonal Dependency Inventory persisted. Results for the RDC-diagnosed patients with endogenous or nonendogenous depression were not so clear-cut; only one significant difference was found between the two groups.

It is noteworthy that the differences were more apparent when smaller subgroups of patients with melancholic-endogenous depression were defined and that the Newcastle scale identified the smallest proportion compared with the RDC, which identified nearly half the sample as having endogenous depression. In this study we used the *DSM-III* criteria for melancholic depression because the data were collected before the introduction of *DSM-III-R*. The criteria in *DSM-III-R* for melancholia now include items similar to the Newcastle criteria, particularly the criterion of "no significant personality disturbance before first major depressive episode." We were not able to examine the effect of this change in diagnostic criteria on personality differences between patients with different types of depression, but we note that Zimmerman et al. (28) found that patients with *DSM-III-R* melancholia had less personality disturbance than those with *DSM-III* melancholia.

The binary view of depression holds that categorical depressive illness has genetic and biochemical determinants and that residual depressive disorders are more determined by an interaction between personality and psychosocial stressors. The binary view is supported by demonstrating "a more stable and well-integrated life-style as reflected by lower rates of premorbid personality disorder" (39, p. 235) in patients with melancholic-endogenous depression.

In this study we have focused on the personality of patients with remitted depression. The extent to which this is a measure of premorbid personality is unclear.

Hirschfeld et al. (40) pointed out that personality measured when the patient has recovered may be distorted in two ways. First, the experience of a depressive episode may adversely affect the patient's personality, leading to scores indicating deviance on recovery. This point is acknowledged, and speculations that the personality features of our recovered depressive patients were accurate reflections of premorbid personality need to be treated with caution. With this caveat in mind, the differences established between the different types of depression can still be interpreted as suggesting that patients with nonmelancholic-nonendogenous depression have a more vulnerable personality. Second, it is possible that the higher scores on personality measures of the patients with nonmelancholic-nonendogenous depression may have reflected residual symptoms rather than personality functioning. This point is conceded, particularly in view of the fact that the patients with nonmelancholic-nonendogenous depression had higher scores on the depression measures, but this would not account fully for differences between groups, as was shown when the severity of depression was partialed out. The relationship between residual symptoms and personality functioning is a complex one. Individuals with dysfunctional personality (judged by high scores on personality measures) may also have symptoms of depression, both during and after the episode. If residual symptoms and personality dysfunction are present they will be correlated, but such a correlation does not necessarily demonstrate causality (in either direction), and that could be resolved only with a longitudinal study. Although it is possible that the higher personality scores of the patients with nonmelancholic-nonendogenous depression may reflect residual symptoms, it is equally possible that residual symptoms result from personality dysfunction, demonstrating the poorer prognosis of sensitive or "thin-skinned" individuals (41).

With this point in mind, our findings offer some support for the binary view of depression and for the idea that the nonmelancholic-nonendogenous type of depression is more likely to have personality vulnerability. The most pronounced differences occurred when the Newcastle system was used to diagnose the different types, in agreement with Zimmerman et al. (39), who reported that this was the only measure of endogeneity to be supported by lower rates of premorbid personality disorder in patients with endogenous depression than in patients with nonendogenous depression.

The personality scales that best discriminated types of depression (especially according to the Newcastle criteria and, to a lesser extent, *DSM-III*) were the interpersonal awareness, separation anxiety, and fragile inner self subscales of the Interpersonal Sensitivity Measure and, to a lesser extent, the emotional reliance on another subscale of the Interpersonal Dependency Inventory and the neuroticism scale of the Eysenck Personality Inventory. These findings sharpen any definition of personality vulnerability in nonmelancholic-nonendogenous depression and support the observations made by Bowlby (42) in describing difficulties associated with the formation and maintenance of affectional bonds in the genesis of depression. Further support for sensitivity to interpersonal interactions contributing to depression comes from two prospective studies. Hirschfeld et al. (40) assessed individuals with no history of mental disorder. A subgroup of 31–41-year-olds who had a first episode of major depression in the 6-year follow-up period scored significantly higher on two of the Interpersonal Dependency Inventory subscales (emotional reliance on another and lack of social self-confidence), which emphasizes the importance of interpersonal dependency as a risk factor for depression. Additionally, in another prospective study design of primigravid women who had not previously been depressed (our unpublished work), high interpersonal sensitivity (measured by using the Interpersonal Sensitivity Measure) was associated with a five-fold higher risk of becoming depressed in the 6 months following childbirth.

The first factor isolated by the principal components analysis discriminated particularly well between types of depression; the patients with nonmelancholic-nonendogenous depression had higher scores. This dependency factor comprises those subscales which have been proposed as reflecting depression-proneness, particularly dependency, interpersonal sensitivity, neuroticism, and an external locus of control. Future research may benefit from focusing on such constructs in quantifying personality vulnerability to depression.

In summary, we have found that patients with melancholic-endogenous and nonmelancholic-nonendogenous depression differ from each other in certain at-risk personality characteristics. We are unable to state whether the personality characteristics of interest are necessarily overrepresented in patients with nonmelancholic disorders or underrepresented in patients with melancholic depression because such a conclusion would require comparison with a normal population. Determining the extent to which personality style is a potential at-risk variable for either type of depression would require a case-control strategy and, ideally, a prospective design. What we have established is that types of depression do differ on such personality dimensions and that such differences are unlikely to reflect any state mood effect, findings compatible with the binary view of depression.

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Depression in Dementia of the Alzheimer Type and in Multi-Infarct Dementia

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The authors used the Hamilton Rating Scale for Depression and a rating of depressed mood to investigate the prevalence of depression in 55 patients with Alzheimer's disease, 37 patients with multi-infarct dementia, and 30 nondemented comparison subjects. The prevalence of depressed mood depended on the severity of dementia as measured by the Mini-Mental State examination and was significantly lower among patients in more severe stages of Alzheimer's disease but not among patients with severe multi-infarct dementia.

(Am J Psychiatry 1990; 147:1484–1487)

Dementia of the Alzheimer's type and multi-infarct dementia account for about 90% of dementias in geriatric cohorts, as demonstrated by neuropathological examination (1, 2). Estimates of depression range from 0% to 87% (3–8) in Alzheimer's disease and from 19% to 27% in multi-infarct dementia (4, 5). Depressive symptoms burden the patients and their caregivers and may be treated with antidepressant drugs (5, 6, 9). Untreated symptoms of depression may be one important factor in the decision to institutionalize a demented patient. Notwithstanding the importance of depression in dementing disorders, to our knowledge no study has directly compared depression in Alzheimer's disease with that in multi-infarct dementia in relation to severity of dementia.

Depression in demented patients can either be defined as depressive disorder (i.e., *DSM-III-R* major affective disorder) or can be described at the level of depressive symptoms. Depressive symptoms can be roughly classified into affective (depressed mood), cognitive (hopelessness, helplessness, worthlessness, memory complaints), somatic (appetite, sleep, libido), and psychomotor categories. Somatic and psychomotor symptoms are particularly common in old age without coexisting depressive disorder and are therefore nonspecific (10). Cognitive symptoms in demented patients are usually not attributed to depression. Affective symptoms are therefore the hallmark of depression in the demented elderly (3, 11).

For that reason, in addition to rating depression by the "gold standard," the Hamilton Rating Scale for Depression (12), which might be a sum score of depressive symptoms of heterogeneous etiology in the demented elderly (13–15), we also investigated depressive affect, rated independently from the Hamilton depression scale. We tried to answer the question of whether depression depends on severity of dementia in Alzheimer's disease and multi-infarct dementia, respectively.

METHOD

The patients, 55 with Alzheimer's disease and 37 with multi-infarct dementia, were inpatients of the neurological department of a geriatric hospital. They took part in a prospective, longitudinal investigation of dementia in the elderly (16) and gave their consent to participate in our investigation after the nature of the procedure had been fully explained.

Dementia was diagnosed according to *DSM-III-R*. Grading of severity of dementia was carried out by using the Mini-Mental State examination (17). According to the criteria of Folstein (18), only patients with Mini-Mental State scores of less than 24 were considered demented. Mild dementia was defined by Mini-Mental State scores ranging from 16 to 23; moderate dementia, by scores from 6 to 15; and severe dementia, by scores less than 6 (16). In the multi-infarct group 21 patients had mild dementia, 12 had moderate dementia, and four had severe dementia; in the Alzheimer's disease group the numbers were 23, 13, and 19, respectively.

All Alzheimer's disease and multi-infarct dementia patients had been selected to fit the diagnostic criteria of *DSM-III-R*. Alzheimer's disease patients also fulfilled the criteria for probable dementia of Alzheimer's type of the Work Group of the National Institute of Neurological and Communicative Disorders and

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TABLE 1. Characteristics of 37 Patients With Multi-Infarct Dementia, 55 Patients With Alzheimer's Disease, and 30 Nondemented Comparison Subjects

Group	Women	Men	Age (years) Mean	SD	Range	Mini-Mental State Score[a] Mean	SD	Range	Hamilton Depression Scale Score[b] Mean	SD	Range	Depressed Mood Scale Score[c] Mean	SD	Range
Multi-infarct dementia	28	9	76.6	7.0	59–85	14.6	6.5	0–23	10.3	4.3	3–19	3.7	1.3	1–7
Alzheimer's disease	48	7	79.4	8.8	58–93	11.5	9.1	0–23	12.4	5.8	2–27	4.1	1.7	1–7
Comparison	28	2	78.2	4.5	69–87	28.6	1.0	27–30	2.4	1.7	0–7	1.5	0.9	1–5

[a] Significant difference among the three groups ($F=55.32$, df=2, 119, $p=0.0000$).
[b] Significant difference among the three groups (Kruskal-Wallis rank ANOVA; $\chi^2=60.58$, df=2, $p=0.0000$).
[c] Significant difference among the three groups (Kruskal-Wallis rank ANOVA; $\chi^2=46.76$, df=2, $p=0.0000$).

Stroke and the Alzheimer's Disease and Related Disorders Association (19). Diagnosis was based on a complete medical and neuropsychiatric examination including history, physical examination, ECG, EEG, CT of the brain, investigation of the ocular fundi, blood count, biochemistry (electrolytes, liver and kidney function, vitamin B_{12}, folic acid), thyroid function, and serological tests for syphilis and AIDS.

The Hamilton Rating Scale for Depression (12) was scored by an independent rater (M.S.), who was blind to symptom rating. Depressed mood was rated on a 7-point scale taken from the Sandoz Clinical Assessment—Geriatric (20) (1=not present, 2=very mild, 3=mild, 4=mild to moderate, 5=moderate, 6=moderately severe, and 7=severe). The item description was, "Dejected, despondent, helpless, hopeless, preoccupation with defeat or neglect by family or friends, hypochondriacal concerns, functional somatic complaints, early waking. Rate on patient's statements, attitude and behavior." This item was rated by the physician in agreement with the patient's nurse. No patient received antidepressants at the time of the investigation or for 2 weeks previously.

Thirty comparison subjects, from a home for the aged in the same district of Vienna as the geriatric hospital, volunteered for the study. Residents in this home were comparable to our chronic care inpatients with regard to education (years in school), socioeconomic status (income per month), gender, and age. They were clinically not demented and scored higher than 26 on the Mini-Mental State.

Statistical analysis was performed at the computer center of the University of Vienna with the Statistical Package for the Social Sciences. Parametric procedures were used only with the dependent variables of age and Mini-Mental State score and included Student's t test and one-way analysis of variance (ANOVA). Depression ratings were evaluated by nonparametric procedures: Mann-Whitney U test (for samples of more than 30 cases, U was transformed into a normally distributed Z statistic), Kruskal-Wallis one-way rank ANOVA (computes H statistic, which has approximately a chi-square distribution), and rank-order correlation coefficient (Spearman's rho). The level of significance was 0.05 (two-tailed).

RESULTS

Characteristics of patients and comparison subjects are shown in table 1. Multi-infarct dementia patients were slightly younger than Alzheimer's disease patients. According to the Mini-Mental State, dementia was slightly more severe in patients with Alzheimer's disease than in patients with multi-infarct dementia ($t=1.81$, df=91, n.s.); we investigated only four severely demented patients with multi-infarct dementia as opposed to 19 severely demented Alzheimer's disease patients. The mean Hamilton depression score was higher for patients with Alzheimer's disease than for patients with multi-infarct dementia, but this difference did not reach significance ($Z=-1.51$, Mann-Whitney U test). Nondemented comparison subjects had significantly lower scores on the Hamilton scale than the two other groups. Mean±SD Hamilton scores did not differ significantly among the various stages of multi-infarct dementia (10.5±4.0 for mild, 9.9±5.3 for moderate, and 10.5±3.0 for severe dementia) ($\chi^2=0.14$, df=2, n.s., Kruskal-Wallis one-way rank ANOVA). The mean Hamilton scores were comparable in mild and moderate Alzheimer's disease (13.1±6.5 and 14.3±5.2), but the mean score was significantly lower in severe Alzheimer's disease (9.9±3.9) ($\chi^2=6.06$, df=2, $p<0.05$, Kruskal-Wallis rank ANOVA).

Depressed mood was comparable in patients with multi-infarct dementia and Alzheimer's disease (mean rank scores=47.32 and 45.95, respectively; $Z=-0.25$, n.s., Mann-Whitney U test). Depressed mood increased slightly from mild to moderate and from moderate to severe multi-infarct dementia ($\chi^2=5.72$, df=2, n.s., Kruskal-Wallis one-way rank ANOVA). Depressed mood differed significantly among the various stages of Alzheimer's disease ($\chi^2=11.39$, df=2, $p<0.005$, Kruskal-Wallis one-way rank ANOVA).

In Alzheimer's disease, depressed mood correlated quite significantly with the Mini-Mental State score: depressive affect was milder in more severe dementia ($r_s=0.50$, N=55, $p<0.001$). In patients with multi-infarct dementia, depressed mood did not correlate with Mini-Mental State scores ($r_s=-0.20$, N=37, n.s.). Correlations between Hamilton depression scale scores and Mini-Mental State scores were nonsignificant in patients with multi-infarct dementia ($r_s=$

−0.02, N=37) but revealed a significantly lower degree of depression in more severe Alzheimer's disease (r_s=0.27, N=55, $p<0.05$). The mood rating correlated quite significantly with the Hamilton depression score in comparison subjects (r_s=0.57, N=30, $p<0.001$) but did not do so in patients with multi-infarct dementia (r_s=0.09, N=37, n.s.) and did so only somewhat significantly in Alzheimer's disease patients (r_s=0.28, N=55, $p<0.05$).

DISCUSSION

This study showed a comparable degree of depression in our samples of multi-infarct dementia and Alzheimer's disease patients by using the Hamilton depression scale. The Hamilton depression scores did not differ among mild, moderate, and severe multi-infarct dementia, but the score was significantly lower in severe Alzheimer's disease. This could be confirmed with the 7-point mood rating that was independent of the Hamilton depression rating. Thus, the significance of depressive affect in the diagnosis of multi-infarct dementia and Alzheimer's disease depends on severity of dementia. Investigating severely demented patients might favor the view that depression is a typical symptom in multi-infarct dementia, but investigations of mild-to-moderately demented patients might find depression more pronounced in Alzheimer's disease. The diagnostic validity of the depression item of the ischemic score (21), which has not been confirmed in all three neuropathological validations of the scale (22–24), is therefore restricted to severely demented patients.

Depression in Alzheimer's disease has been associated with pathology of the noradrenergic, dopaminergic, serotonergic, and cholinergic systems (25–29). A recent study demonstrated the relative preservation of cholinergic activity in several subcortical brain regions of depressed Alzheimer's disease patients and suggested that there is a threshold for central cholinergic function below which the clinical expression of depression is not possible (26). To our knowledge, ours is the first study to show a lower prevalence of depression in severe Alzheimer's disease. However, it is also possible that with increased loss of neurons, the patients might no longer be concerned about their illness, with resultant blunting of affective response (30). The latter mechanism might also work in multi-infarct dementia, but a severe enough degree of dementia is rarely found in multi-infarct dementia. We found that 13 Alzheimer's disease patients were not testable with the Mini-Mental State, compared to only one patient with multi-infarct dementia (who was not rated as depressed).

Depression in stroke patients has been associated with lesion location, lesion volume, psychological reactions to physical impairment, and disruption of the noradrenergic and/or serotonergic system (31–35). The correlation of lesion volume and physical impairment with depression might explain the slightly higher rates of depressive affect in patients with more severe multi-infarct dementia. We found no clear association between lesion location (on cranial CT) and depression in multi-infarct dementia.

Three other clinical studies compared depression in multi-infarct dementia and in Alzheimer's disease. Reding et al. (4), investigating outpatients, found depression more common in Alzheimer's disease. Danielczyk (36) described a higher rate of antidepressant treatment in early Alzheimer's disease, and a higher rate of antidepressant treatment in advanced multi-infarct dementia. Cummings et al. (5), who investigated multi-infarct dementia and Alzheimer's disease patients with a degree of dementia comparable to that in our patients, found depression more common in multi-infarct dementia. They accepted Hamilton scores of 9 or above as indicative of some degree of depression and found that 17% of the Alzheimer's disease patients, compared to 60% of the patients with multi-infarct dementia, were in the depressed range; comparable figures in the present study were 80% (N=44 of 55) and 70% (N=26 of 37), respectively. There are at least four possible explanations for the higher rate of depression in Alzheimer's disease patients in our investigation. We studied chronic inpatients, who are said to show a higher degree of depression (8, 37); studies using information from caregivers rather than self-observations from demented patients also found higher rates of depression (7); on average, our patients were 9 years older than those of Cummings et al.; and the latter study used the ischemic score (21), which contains the item "depression," to discriminate between multi-infarct dementia and Alzheimer's disease and thus introduced logical circularity because depressed patients tended to be classified as having multi-infarct dementia.

Studies investigating mild stages of Alzheimer's disease have consistently found high rates of depression (4–8, 38). The exception is the study by Knesevich et al. (3), in which the Hamilton and Zung depression scales were administered to patients with early Alzheimer's disease who, by definition, had no history of depression "at any time during their lives." Lazarus et al. (6) found that 20% of mildly demented outpatients with Alzheimer's disease had Hamilton depression scores higher than 18, which is the usual criterion for including depressed inpatients in antidepressant drug trials. Using this cutoff score, we found only one (3%) of our multi-infarct dementia patients and seven (13%) of our Alzheimer's disease patients in the depressed range. We thus speculate that severity of depression is even higher in mildly demented Alzheimer's disease outpatients than in our Alzheimer's disease inpatients and that it decreases progressively during the course of the disease. The latter speculation must be proven in a longitudinal study. Whether such a release from depression in severe Alzheimer's disease is related to the progressive loss of cholinergic activity must be proven in clinicopathological studies.

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Value of the DST for Predicting Response of Patients With Major Depression to Hospitalization and Desipramine

J. Craig Nelson, M.D., Carolyn M. Mazure, Ph.D., and Peter I. Jatlow, M.D.

The authors examined the value of the dexamethasone suppression test (DST) for predicting response of patients with unipolar, nonpsychotic major depression to 1 week of hospitalization without antidepressant drugs and to a 4-week trial of desipramine at a fixed plasma level. The rates of response to hospitalization without drug treatment (defined as a score of 12 or less on the Hamilton Rating Scale for Depression) were not significantly different for the patients with a positive DST and those with a negative DST. This finding differs from those of prior studies of the DST and response to placebo. The responses of the DST-positive and DST-negative patients to desipramine also did not differ, a finding that replicates those in some prior reports.

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The dexamethasone suppression test (DST), which has been widely studied as a biological marker of depression and suggested as a test for melancholia (1), has also been proposed as a predictor of outcome. In 1979 Brown et al. (2) suggested that patients with a positive DST (i.e., who did not suppress cortisol) were more responsive to somatic treatment than depressed patients with a negative DST, a finding that was quickly replicated (3, 4). Brown et al. (5) further suggested that patients with a positive DST were more likely to respond to noradrenergic antidepressants (desipramine and imipramine) than to more serotonergic drugs such as amitriptyline and clomipramine. Subsequently, numerous investigators explored the value of the DST for predicting drug response; however, as other reviewers have concluded (6–8), the findings with respect to both hypotheses—that patients with positive DST results have a better response to somatic treatment generally and that they have a better response to noradrenergic antidepressants specifically—have been contradictory.

A more consistent finding has been the association of a positive DST with poor response to placebo. Peselow et al. (9) reported that in depressed outpatients treated with placebo for 3–6 weeks, none of seven nonsuppressors responded, compared with seven (58%) of 12 suppressors. In a subsequent inpatient sample, Peselow et al. (10) noted that none of five nonsuppressors and seven (58%) of 12 suppressors responded to 3–4 weeks of placebo treatment. Brown et al. (11) found that only one (8%) of 12 depressed outpatients who were nonsuppressors was responsive to placebo, while 16 (59%) of 27 suppressors were placebo responders. Consistent with these reports, Preskorn et al. (12) noted greater drug-placebo differences in DST-positive children treated for depression than in DST-negative patients. Georgotas et al. (13) failed to find a difference in response to placebo in patients with positive and negative findings on the DST; however, in their elderly sample, rates of response to placebo were low in both groups.

A positive DST has also been associated with less favorable response to psychosocial treatment. Rush (14) found that none of five depressed outpatients who were nonsuppressors of cortisol responded to cognitive therapy, while eight (89%) of the nine suppressors were responsive. Recently, Robbins et al. (15) examined response to 6 weeks of psychosocial treatment without somatic therapy in adolescents hospitalized for depression and reported that none of seven DST nonsuppressors responded, while 18 (58%) of 31 suppressors improved with this treatment. These data suggest that the DST may be of value in identifying patients who are unlikely to respond to placebo or psychosocial treatments and for whom somatic treatment is likely to be required.

In the current study we examined the value of the DST for predicting response to a 1-week period of hospitalization without antidepressant treatment and response after a 4-week trial of desipramine at a fixed plasma level. We were particularly interested in whether a positive DST would predict poor response to hospitalization without antidepressant treatment just as it has predicted poor response to placebo in prior studies.

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METHOD

The methodology of the study has been described in detail elsewhere (16). Briefly, the study was conducted in two phases. In phase 1 response was assessed after 1 week of hospitalization during which no antidepressant medication was administered. In phase 2 response was determined after a 4-week trial of desipramine in which the dose was rapidly adjusted to achieve a therapeutic plasma level. All but one of the nonresponding patients in phase 1 entered phase 2; however, phase 2 also included other patients who had not been rated during the initial 3 days of hospitalization.

Subjects

Patients consecutively admitted to a general hospital adult psychiatric unit who had nonpsychotic, unipolar major depression according to *DSM-III* criteria were included. Psychotic and bipolar patients were excluded, as were patients with schizophrenia, organic brain disease, active medical illness, or recent alcoholism, drug abuse, or eating disorder. In addition, patients having medical conditions or receiving medications known to affect the DST (1, 8) were excluded.

Fifty-one patients (36 female and 15 male) with major depression were included in phase 1. Only patients whose initial rating was done within 3 days of admission were included in this phase because response to hospitalization was rated at 1 week. The mean±SD age of the sample was 43.0±15.7 years. The mean±SD duration of the episode was 27±71 weeks. The mean±SD score on the 17-item Hamilton Rating Scale for Depression (17) was 22.9±5.9. Eighteen of the 51 patients met the *DSM-III* criteria for melancholia. Thirteen of the 51 patients had preexisting nonaffective psychiatric disorders, i.e., secondary depression. Fourteen patients had coexisting dysthymia, and 29 of the 51 had recurrent depression.

In phase 2 patients with major depression who had failed to respond during the first week of hospitalization without antidepressant medication began drug treatment. Additional exclusion criteria included a history of adverse reactions to desipramine or prior use of desipramine during this episode. Fifty-seven patients (46 female and 11 male) began desipramine treatment. (This number included 32 nonresponders from phase 1 and 25 other patients who met the entry criteria but had not been rated within 3 days of admission as phase 1 required.) The mean age of the patients in phase 2 was 48.0±16.0 years. Their mean initial Hamilton depression score was 24.1±4.5, and the mean duration of the depressive episode was 38±70 weeks. Of the 57 patients, 26 were melancholic according to *DSM-III* criteria, 19 had secondary depression, 14 had coexisting dysthymia, and 38 had recurrent depression.

Procedures

Symptoms were assessed by a research nurse who was blind to the DST results, using the Yale Depression Inventory, for which the reliability of individual items has been previously reported (18). The inventory provides a structured interview for the 17-item Hamilton depression scale and the severity and improvement items from the Clinical Global Improvement (CGI) scale (19), and it rates the *DSM-III* criteria for melancholia, psychotic depression, and panic disorder. A shortened version of the inventory that included the CGI and the Hamilton scale was then repeated after 1 week of hospitalization without desipramine and weekly throughout the 4-week desipramine trial.

In phase 1 no psychotropic medications were administered except lorazepam, which was allowed for sleep and agitation. In phase 2 plasma samples drawn 24 hours after a standardized milligram-per-kilogram desipramine dose were used to calculate the dose necessary to achieve a target plasma desipramine level of 140 ng/ml (20). The full calculated dose (50–500 mg/day) was begun by the third day of drug treatment and continued for 4 weeks. Plasma samples were obtained during weeks 2, 3, and 4 and were averaged to determine steady-state levels. Plasma concentrations of desipramine were determined by using a modification of a high-performance liquid chromatography method (21). The mean±SD desipramine plasma level obtained was 164±46 ng/ml.

The DST was given before drug treatment, usually during the first week of hospitalization (an average of 4.6 days afer admission). One milligram of dexamethasone was administered orally at 11:00 p.m. Blood samples were drawn the following day at 8:00 a.m. and 4:00 p.m. from all but seven patients; samples from these seven were obtained at 4:00 p.m. and 11:00 p.m. For all patients, two samples were obtained and the highest cortisol value was used. In the early part of the study, serum cortisol levels were determined with a fluorometric technique (22). Recognizing that this procedure has some nonspecific fluorescent background, we used a higher cutoff of 7 μg/dl to define nonsuppression of cortisol (23). In the second half of the study, cortisol levels were determined with a radioimmunoassay technique (GAMMACOAT, Travenol-Genentech Diagnostics). For these patients, the commonly used cutoff of 5 μg/dl was applied (1). Although a higher cutoff was used for the fluorometric method, only three patients had cortisol levels of 6 or 7 μg/dl that were affected by the difference.

Definition of Response and Data Analysis

In phase 1 the primary criterion for response was a Hamilton depression score of 12 or less after 1 week of hospitalization. A dichotomous rating of response/nonresponse was selected, since a decision whether to begin giving antidepressants was required. The score of 12 or less had been used in a prior study of placebo

TABLE 1. DST Results and Response of Patients With Major Depression to Hospitalization and Desipramine

	After 1 Week of Hospitalization (Phase 1) (N=51)				After 4 Weeks of Desipramine (Phase 2) (N=42)			
	Responders[a]		Nonresponders		Responders[b]		Nonresponders	
DST Result	N	%	N	%	N	%	N	%
Negative	8[c]	32	17	68	16[c]	73	6	27
Positive	10[c]	38	16	62	11[c]	55	9	45

[a] Score of 12 or less on the Hamilton Rating Scale for Depression.
[b] Rating of much or very much improved on the Clinical Global Improvement scale.
[c] Chi-square analysis of response by DST result not significant.

response (24), patients with scores of 12 or less usually did not require drug treatment, and this score best divided patients into those with no or mild depression and those with moderate to severe depression. We also identified patients who improved by at least 50% on the Hamilton scale. For those identified as hospital responders (score of 12 or less), we determined whether the apparent response was sustained for the remainder of the hospitalization. The chi-square test with Yates' correction or Fisher's exact test was used to assess the relationship of the DST results and 1-week response.

In phase 2 the primary definition of response was a dichotomous split in the CGI ratings (no or minimal improvement versus much or very much improvement). A patient had to complete the entire 4-week trial before he or she was judged to be a nonresponder (except for three patients whose depressive symptoms worsened before completion of the trial). Patients who improved, met the response criterion, and were discharged before 4 weeks were included with the responders. Of the 57 patients who began desipramine, eight developed side effects, seven left the hospital prematurely for nonclinical reasons, and 42 completed the desipramine trial. Dropouts were somewhat but not significantly less likely than completers to be nonsuppressors of cortisol (three of 15 versus 20 of 42; $\chi^2=2.45$, df=1, p=0.12).

RESULTS

A total of 76 patients were included in either phase 1 or phase 2, and 34 of them had a positive DST. The frequencies of a positive DST were nearly identical for the fluorometric and radioimmunoassay methods of cortisol determination: 18 of 40 (45%) and 16 of 36 (44%), respectively. Associations of the pretreatment DST findings with descriptive features were examined in this total group. A positive DST was not significantly correlated with age, sex, global severity, episode duration, or recurrence of depression. There were trends for an association of the DST finding with the total Hamilton depression score at admission (r=0.20, df=74, p=0.08), with the presence of melancholia (r=0.16, df=74, p=0.16), and with reported weight loss (r=0.20, df=74, p=0.08), but in no case was the correlation substantial or statistically significant. Lorazepam was used for sleep or anxiety by 31 patients, but neither the use of lorazepam nor the lorazepam dose was significantly correlated with DST results.

To test the possibility that stress at the time of admission might have affected the DST findings, we examined DST results in relation to the timing of the test. In the total group the DST was done an average of 5.6 days after admission to the hospital and 4.6 days after admission to the psychiatry unit (some patients were first admitted to a medical unit). Neither time interval was significantly correlated with DST results. Of the 20 patients who were given the DST within 2 days of admission, 50% (N=10) were nonsuppressors of cortisol, in comparison with 43% (N=24) of the 56 patients who had the DST after 2 days; this difference was not significant ($\chi^2=0.08$, df=1, n.s.).

Phase 1: The DST and Response to Hospitalization

Twenty-six of the 51 patients in phase 1 had a positive DST, and 10 of these 26 patients were responsive to hospitalization; eight of the 25 DST-negative patients were responsive ($\chi^2=0.03$, df=1, n.s.) (table 1). When hospital response was defined as 50% improvement in the Hamilton depression score, six of the 26 DST-positive patients and four of the 25 DST-negative patients were responders to hospitalization, again not a significant difference ($\chi^2=0.08$, df=1, n.s.). Four patients had Hamilton depression scores of 12 or less on admission (the scores were 12, 12, 11, and 9); two of the four had positive DST results. We retained these patients in the study, since they met the criteria for current major depression, they required hospitalization, and we anticipated that some of them might worsen during the first week. However, when these patients were dropped from the analysis because of their low depression scores, the findings were unaffected: eight (33%) of the 24 DST-positive and six (26%) of the 23 DST-negative patients were hospital responders ($\chi^2=0.05$, df=1, n.s.).

To control for the possibility that concurrent medications not recognized as affecting the DST might have interfered with the test, the 19 patients receiving these drugs were dropped and the analysis redone. Again, there was no suggestion of a relationship: four (31%)

of 13 DST-positive and seven (37%) of 19 DST-negative patients were hospital responders (Hamilton depression score of 12 or less) ($\chi^2=0.00$, df=1, n.s.). Lorazepam dose was higher for the nonresponders (r=0.32, df=74, p=0.02), suggesting that there was greater use of lorazepam by the patients who did poorly. However, the partial correlation of DST results and hospital response remained nonsignificant when lorazepam dose was controlled.

Hospital responders (Hamilton depression score of 12 or less) were further examined to determine whether their response was sustained. Twelve of the 18 patients continued to do well and were discharged without having taken any medication. Six patients appeared to minimize subjective symptoms, but they were observed to show persistent signs of depression, such as anhedonia or depressive rumination, which led to the clinical decision to initiate antidepressant treatment. Mean±SD depression scores after 1 week did not differentiate these six from the other 12 responders (8.6±3.3 and 8.0±2.8, respectively), nor did the use of the 50% improvement criterion. Persistent symptoms were noted in five of the 10 patients who had a positive DST and in one of the eight who had a negative DST, a difference that was suggestive but not significant (p=0.12, one-tailed, Fisher's exact test). When the data on the six patients who failed to sustain improvement were grouped with the data on the other nonresponding patients, DST results remained unrelated to hospital response ($\chi^2=0.17$, df=1, n.s.).

Since melancholia had been shown to be strongly predictive of poor hospital response (16), we thought a relationship between the DST and response to hospitalization might be more obvious in nonmelancholic patients. However, this was not the case; the findings were unaffected by the deletion of data on the melancholic patients.

The findings were also examined to see whether the method of cortisol determination affected the results. However, the results with the fluorometric and the radioimmunoassay methods were nearly identical.

Phase 2: The DST and Response to Drug Treatment

Forty-two of the 57 patients who began phase 2 completed the trial. Twenty of these 42 patients had positive DST results. When the CGI was used to rate response, 11 of the 20 DST-positive patients were responsive to desipramine, and 16 of the 22 DST-negative patients were responsive to desipramine ($\chi^2=0.76$, df=1, n.s.) (table 1). When patients taking concurrent medications were dropped from the analysis, six of 10 DST-positive patients and nine of 13 DST-negative patients were responsive to desipramine ($\chi^2=0.00$, df=1, n.s.). Whether a Hamilton score of 12 or less was used alone or with a CGI rating of 2 or less to define response, there was no substantial difference in the findings.

When the last available CGI ratings of the eight patients who failed to complete the desipramine trial because of side effects were included in the analysis, 11 (50%) of 22 DST-positive and 16 (57%) of 28 DST-negative patients had favorable outcomes ($\chi^2=0.05$, df=1, n.s.).

Steady-state blood levels of desipramine in the patients who completed phase 2 appeared to be adequate (25) in all but two, whose levels were marginal: 106 and 91 ng/ml. Exclusion of the data for these two patients had no effect on the relationship of the DST results and response. This relationship was also unaffected by the method of cortisol determination.

DISCUSSION

DST results did not predict outcome in these depressed inpatients. The lack of prediction of drug response does not seem surprising given the contradictory earlier reports and the negative results of a study that used desipramine specifically (26). As in three prior studies that used standardized ratings after a fixed interval of treatment (13, 26, 27), we found that DST-positive patients were slightly less responsive. The trend for DST-positive patients to be more severely ill may help to explain why they were less improved after 4 weeks of desipramine treatment.

The lack of an association between DST results and response to hospitalization differed from the findings of prior studies in which a positive DST result predicted poor response to psychosocial treatment or placebo. We did not find DST-positive patients significantly less responsive, and the actual percentage who responded was very similar or slightly higher for these patients (38% versus 32%). Our results did not appear to be affected by age, sex, episode duration, recurrence, concurrent medications, lorazepam dose, timing of the DST in relation to admission, or the method of cortisol determination. The overall rate of response to hospitalization (35%) appeared sufficient for a difference in hospital response rate to have been detected if present.

The only suggestive positive finding for the DST in this study was that patients who reported initial improvement with hospitalization but were observed to show persistent depressive symptoms during the second and third weeks of hospitalization were more likely to have had a positive DST. However, even this relationship was weak and was lost entirely if these patients were grouped with other nonresponders.

Our results differ from those of the five previous studies (9–11, 14, 15) which found that a positive DST predicts poor response to both placebo and psychosocial treatment in depressed patients and that somatic treatment is likely to be needed. We cannot explain the difference between our findings and the results of these earlier studies. We note, however, that the numbers of nonsuppressors in the five prior studies were quite low (seven patients or fewer in four of the studies, or a total of 36 in the five studies). In our study 26 nonsuppressors were assessed for response to hospitalization, a number only slightly lower than the total in the five earlier studies combined.

The rate of response to hospitalization in our sample, 35%, was not significantly different from the average response rate of 45% in the five previous studies of placebo or psychosocial treatment ($\chi^2=1.00$, df=1, n.s.); however, the percentage of nonsuppressors in our phase 1 sample (51%) was substantially higher than the average in the previous studies, which was 28% (36 of 127; $\chi^2=7.25$, df=1, $p<0.01$). It is possible that even though recognized exclusion criteria for the DST were used, the rate of cortisol nonsuppression was inflated by other unidentified factors, and this may have obscured a relationship of the DST with response. However, we suspect that this higher rate of nonsuppression reflects the greater severity of illness of hospitalized patients, since this rate is consistent with rates reported for depressed inpatients (8). In addition, this was a consecutive series of patients admitted to a general hospital psychiatric unit. Even if other unidentified factors affecting the DST were present, our sample seems representative of patients in a general hospital setting and useful for testing the predictive value of the DST in this setting. Our data suggest that DST results do not predict response to either hospitalization or antidepressant drug treatment of adults hospitalized for major depression.

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Antidepressant Pharmacotherapy of Depression Associated With Multiple Sclerosis

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In a double-blind clinical trial involving 28 patients with multiple sclerosis and major depressive disorder, 14 patients were randomly assigned to a 5-week trial of desipramine and individual psychotherapy and 14 to placebo plus psychotherapy. Clinical judgments indicated that patients treated with desipramine improved significantly more than the placebo group. This was confirmed by scores on the Hamilton Rating Scale for Depression but not by Beck Depression Inventory scores. Side effects limited desipramine dosage in half of the treated patients. The authors conclude that desipramine has a modest beneficial effect in serious depression associated with multiple sclerosis but that side effects may be more of a limiting factor than in patients without medical or neurologic disease.

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In their 1926 paper, Cottrell and Wilson (1) interviewed 100 consecutive multiple sclerosis patients and concluded that 100% of them had experienced affective symptoms as a sign or symptom of disease activity. They concluded that alteration in experienced mood or expressed affect was a "basal" sign of the disease, as reliable in diagnostic reasoning as more traditional neurologic findings, such as spasticity or weakness.

Later controlled studies have generally corroborated the purported association between multiple sclerosis and disorders of affect. Unipolar depressive episodes have been reported to occur more commonly among multiple sclerosis patients than among patients with equally disabling neurologic diseases, such as amyotrophic lateral sclerosis, temporal lobe epilepsy, muscular dystrophy, and spinal cord injury (2–7). Bipolar disorder has also been described as occurring with an unusually high frequency among multiple sclerosis patients (8, 9), as have euphoria (10–13) and pathological laughing and weeping (14, 15). This last syndrome is unusual in that there occurs a neurologically based dissociation between expressed and perceived affect, so that patients may weep when cheerful and laugh when depressed.

In this report, we have chosen to focus on the psychopharmacologic therapy of depressive episodes among multiple sclerosis patients. This focus is in keeping with our broader interests in the applicability of psychopharmacologic and psychotherapeutic regimens to the medically ill. Despite clinical epidemiological data indicating the frequent occurrence of depressive symptoms among patients with a variety of medical illnesses, few treatment trials exist (16–18). In a double-blind trial of trimipramine among mixed general medical patients with depression, Rifkin and colleagues (19) found evidence for efficacy of the antidepressant but noted that depression also improved in the placebo group when the physical illness improved. When Popkin and colleagues (20) reviewed their experience with antidepressant pharmacotherapy of 78 mixed medical inpatients with depression, they found a relatively low response rate (40%) combined with a high rate of unacceptable side effects (32%). With respect to patients with specific neurologic diseases, controlled studies of antidepressant pharmacotherapy exist only for poststroke depression and depression associated with Parkinson's disease; both studies (21, 22) indicated a beneficial effect for nortriptyline.

With regard to the depressive episodes associated with multiple sclerosis, most clinical studies have not used standardized diagnostic criteria. In one study (23) that described Research Diagnostic Criteria (RDC) subtypes for 20 multiple sclerosis patients with RDC major depressive disorder, a heterogeneous range of subtypes was present, with a preponderance of "situational" diagnoses. There is evidence that approximately 20% of multiple sclerosis patients with depressive diagnoses have received their affective diagnoses well before the first multiple sclerosis symptom (2). The depressive episodes tend to be related in time to exacerbations of the multiple sclerosis, and they tend

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to occur more often in patients with cerebral involvement in the disease, as opposed to those with primarily spinal cord involvement (5, 24). There is preliminary evidence that multiple sclerosis patients with depressive disorders demonstrate more structural brain disease in limbic areas than do other multiple sclerosis patients (25).

There are few studies regarding appropriate therapies for the depressive episodes that occur among multiple sclerosis patients. Tricyclic antidepressants are widely used in clinical practice, but to our knowledge, neither controlled nor open trials concerning their efficacy have been published. We designed a double-blind, placebo-controlled study to assess whether desipramine plus psychotherapy would be more effective in such patients than would placebo plus psychotherapy.

METHOD

Subjects and Procedure

The Multiple Sclerosis Research Group at the University of Rochester provides neurologic care for 450 patients from Monroe and neighboring counties. During the past 3 years, all patients with definite multiple sclerosis according to research criteria (26) were screened for affective disorders during routine clinic visits. Patients with clinical evidence of affective symptoms were interviewed with the Schedule for Affective Disorders and Schizophrenia (SADS) (27). Psychiatric diagnoses were made in accordance with the RDC (28). Patients who met the criteria for definite major depressive disorder were invited to participate in the therapeutic trial. Informed consent was obtained from the patients who agreed to participate. The duration of the trial was targeted as 30 days, but every subject who reached 14 days or more was included in the data analysis.

Patients who entered the study were assessed either in the Clinical Research Center of the University of Rochester or in the Department of Neurology outpatient clinic before the initiation of pharmacotherapy. Baseline clinical interviews were performed, as well as evaluations with the Hamilton Rating Scale for Depression and the Beck Depression Inventory and neurologic examinations. Ratings of neurologic function were performed by using Kurtzke's Expanded Disability Status Scale (29). This scale provides an objective rating of overall disability in multiple sclerosis patients, ranging from 0 (normal neurologic status) to 9.5 (totally helpless bed patient) in steps of 0.5.

In order to control for the confounding factor of clinician contact with the patients, as well as to address the ethical issue of committing seriously depressed individuals to a placebo group, all patients were assigned to a concomitant, very short-term psychotherapy. We have described this short-term psychotherapy for multiple sclerosis patients in another publication (23). In brief, the therapy involves assigning the patients to a management strategy that is either supportive and medical in orientation, interpersonal and social in orientation, or insight oriented. The assignments were made by clinical judgment at the time of initial assessment, and the therapies were conducted in weekly 45-minute sessions by one of the investigators (R.B.S.). These sessions were conducted without knowledge of whether the patient was taking active drug or placebo. The assignment of strategies was approximately equal between the two groups of active drug and placebo.

Desipramine, 25 mg, and placebo were provided in identical capsules. The hospital pharmacy dispensed the medication (either desipramine or placebo) according to a pre-randomized schedule when patients consented to participate in the drug trial. During the first 7 days of the study, each patient's dose was raised at 2-day intervals to six capsules per day (3 b.i.d.) or to the maximum daily dose permitted by side effects. At the first outpatient visit, a serum desipramine level was determined in the clinical chemistry laboratories at Strong Memorial Hospital by using an extraction and chromatography method. The serum levels were reviewed by an outside observer during the second week, and dose adjustments were provided to the primary therapist (R.B.S.) with the aim of moving the serum level into the 125–200 ng/ml range. Dose adjustments were also made for placebo patients. Additional serum levels were checked at week 2.

The Beck Depression Inventory and Hamilton Rating Scale for Depression were administered by one of us (N.M.W.) during each weekly visit. A blind clinical judgment concerning the occurrence of significant clinical improvement was made by the primary therapist at the conclusion of the study. In order to be judged improved, a patient was required to demonstrate sufficient improvement in depressive features so as to permit a definite improvement in psychosocial function. We determined in advance that these blind clinical judgments concerning significant improvement in psychosocial function would constitute the primary outcome variable on which to base data analyses.

Patients were excluded from the study if the depressive episode had occurred during a period of acute corticosteroid administration. Patients were excluded from the study if they were taking psychotropic drugs. Baclophen and anticholinergic drugs for bladder management were permitted. Otherwise, we attempted to enroll all patients who met the criteria for the study.

Statistical Analyses

Primary reliance for analysis of outcome was placed on blind clinical judgments of amelioration in depressive symptoms sufficient to permit objective improvement in psychosocial function. After the drug/placebo code was broken, a two by two table was constructed with all patients categorized as improved or not improved. Fisher's exact test was used to examine differences between the groups.

TABLE 1. Clinical Features of Patients With Multiple Sclerosis and Major Depressive Disorder Who Received Desipramine or Placebo

Patient	Age (years)	Sex	Kurtzke Disability Score	Beck Depression Score		Hamilton Depression Score		Desipramine		Judgment of Outcome
				Week 0	Week 5	Week 0	Week 5	Dose (mg/day)	Highest Serum Level (ng/ml)	
Desipramine (N=14)										
1	55	F	—[a]	15	19	33	18	200	177	Improved
2	51	F	1.5	29	19[b]	37	20	150	93	Not Improved
3	54	F	2.0	21	13	24	11	150	107	Improved
4	46	M	2.5	15	6	26	7	150	205	Improved
5	34	F	3.0	19	16	28	17	200	65	Improved
6	38	F	3.5	17	28	24	18	100	—[c]	Improved
7	22	F	3.5	14	4[b]	23	7	75	208	Improved
8	28	F	3.5	8	2[b]	40	3	125	57	Improved
9	27	F	5.0	17	3	21	7	125	274	Improved
10	30	M	5.5	12	7	24	21	150	145	Not improved
11	37	F	6.0	25	9[b]	34	10	125	69	Improved
12	34	F	6.5	18	7	25	12	75	112	Improved
13	48	F	7.0	28	21	31	18	150	229	Improved
14	25	F	8.0	20	6[b]	26	9	125	31	Improved
Placebo (N=14)										
15	37	F	2.0	5	4	6	18	—	—	Not improved
16	44	F	2.5	16	6	21	3	—	—	Improved
17	45	F	2.5	10	—[c]	21	34[b]	—	—	Not improved
18	44	M	2.5	14	14	25	12	—	—	Improved
19	33	F	3.0	31	26	33	30	—	—	Improved
20	45	M	3.5	9	4	20	7	—	—	Improved
21	24	F	3.5	16	3	30	21	—	—	Improved
22	22	F	3.5	28	36	39	48[b]	—	—	Not improved
23	33	M	6.0	14	1	28	0	—	—	Improved
24	36	F	7.0	20	16	25	28	—	—	Not improved
25	30	F	7.0	18	22	30	28[b]	—	—	Not improved
26	37	F	7.5	35	26	24	16	—	—	Not improved
27	75	F	8.0	24	17	34	32	—	—	Not improved
28	43	F	8.5	21	26	13	14	—	—	Not improved

[a] Kurtzke score was not meaningful (patient had superimposed conversion disorder).

[b] Protocol terminated before fifth week.

[c] Patient refused the test.

Comparisons between drug and placebo groups on the Hamilton and Beck scales were conducted with the Wilcoxon rank sum test. This statistical test was applied to a comparison of *change* in group medians on the two scales during the course of the study. The results of these analyses are described in the text.

RESULTS

During the 3-year period of case finding for this study, 39 patients were seen in the multiple sclerosis clinic who met the RDC for major depressive syndrome, not complicated by concurrent corticosteroid therapy. Seven patients who met the criteria did not enter the study. Six of these patients (five women and one man) refused to participate, and one patient had begun antidepressant therapy elsewhere and did not wish to discontinue medications.

Two patients were dropped from the study during the first 7 days of the drug trial and were not included in the data analyses. Both stated that they had decided against taking medications, but neither indicated that side effects had been a problem. Another two patients were dropped because it was determined during the neurologic evaluation that they did not have definite multiple sclerosis according to research criteria.

Twenty-eight patients completed the drug treatment protocol, defined by participation in the 30-day protocol for at least 2 weeks. Raw data and demographic features for these patients are presented in table 1, with the patients categorized as to drug treatment or placebo and rank ordered according to neurologic disability (from mildest to most severe). The mean±SD study duration was 29.8±5.1 days in the drug group and 29.7±5.8 days in the placebo group. The desipramine levels recorded in table 1 were the highest levels attained by each patient; they were 8:00 a.m. serum levels, without a prior morning dose of medication. Corresponding desipramine dose per 24 hours is also presented in table 1. The mean dose for the group was 123.2±60.8 mg/day, and the highest mean serum level was 136.3±36.1 ng/ml. Seven of the desipramine patients were unable to reach the serum level goal of 125 ng/ml because of side effects.

As depicted in table 1, there were 12 women

(85.7%) and two men (14.3%) in the desipramine group and 11 women (78.6%) and three men (21.4%) in the placebo group. The mean age of the desipramine group was 37.8 years (range, 22–55), while it was 39.1 years (range, 22–75) for the placebo group. None of these differences in demographic characteristics between groups was significant.

The Kurtzke Expanded Disability Status Scale scores provide an interesting dimension to these results. The range of disability among patients in the study spanned almost the entire range of scores, from 1.5 to 8.5, indicating that the patients with the mildest illness had essentially normal results on neurologic examinations, while the most severely ill were bedridden and had minimal self-care ability. The mean scores of 4.4±2.1 for the desipramine group and 4.8±2.4 for the placebo group were not significantly different.

Examination of the relationship between the severity of depression (Beck scores) and the severity of neurologic disability (disability status scores) is important for understanding the potential relationship between depression and severity of disability. At the beginning of the study, the Spearman correlation coefficient for the Beck and disability status scores was 0.27 for all subjects, and at the conclusion of the study it was 0.20. From these data we conclude that there was only a weak tendency for more severe depression, as measured by Beck scores, to be associated with more severe neurologic disability, as measured by the disability status scores. In the two subjects in the desipramine group who *failed* to improve with regard to depression according to blind clinical judgment, the disability status scores were not particularly high (1.5 and 5.5). It seems unlikely that neurologic disability alone could account for the depressive phenomena under study.

According to the results of the blind clinical judgments, there was significant improvement in depression in 11 of 13 patients in the active drug group and in six of 14 patients in the placebo group. This difference in clinical improvement was significant ($p=0.05$, Fisher's exact test). (The 14th patient in the active drug group was significantly improved at 35 days, but this judgment was not made blindly. Her depression had become so severe that by day 14 it was not considered ethical to continue the double-blind trial, although she wished to continue in the study in all other respects. She was not included in this data analysis.)

We reviewed the clinical histories of these patients for evidence of affective disorders that might have antedated the clinical onset of multiple sclerosis. This enterprise was made difficult by anamnestic problems in dating first symptoms of multiple sclerosis, as well as by such problems in making retrospective psychiatric diagnoses. Still, four of the 14 patients assigned to drug therapy and three of the 14 assigned to placebo gave histories of significant depressive episodes at some time before their first multiple sclerosis symptoms. These proportions are quite comparable between groups.

To assess the rates of improvement in depressive symptoms in drug and placebo groups on the rating scales, we performed a nonparametric comparison of change in mean scores between groups. The desipramine patients improved on the Beck scale from an initial mean score of 18.4±5.9 to a final mean score of 11.4±8.0. They improved on the Hamilton scale from a mean±SD of 28.3±5.8 to 12.7±5.8 at study termination. The corresponding scores for the placebo patients were 18.6±8.6 and 15.5±11.3 on the Beck scale and 24.9±8.6 and 20.1±13.6 on the Hamilton scale. A comparison of the magnitude of change between groups by using the Wilcoxon rank sum test indicated that the difference between drug and placebo was not significant for the Beck scores ($W=130.5$, $p=0.16$). The difference was significant, however, for improvement in depression as measured by Hamilton scores ($W=254.0$, $p=0.02$).

Seven patients in the placebo group and 12 in the desipramine group had at least one side effect. Postural hypotension, dry mouth, and constipation were the most commonly reported side effects, but it is worth noting that dry mouth occurred with equal frequency in the placebo ($N=5$) and desipramine ($N=5$) groups. Other side effects were jitteriness, edema, dizziness, and rash. In only three of the desipramine patients did side effects preclude the attainment of the initial target desipramine dose (125 mg/day). Side effects did preclude our reaching the targeted serum level of 125 ng/ml in seven of the desipramine patients. This did not seem to be a major factor in clinical outcome, however, since six of these seven still were judged significantly improved in the blind ratings of depression.

DISCUSSION

To our knowledge, this research represents the first double-blind, controlled study of antidepressant medication in multiple sclerosis patients with major depressive disorder diagnosed by the SADS and RDC. Such a report is of some clinical relevance for practicing psychiatrists who treat multiple sclerosis patients. It is also of heuristic interest, since the neuropsychopathologic processes underlying affective disturbance in multiple sclerosis patients may differ from such processes in general psychiatric patients. It could well be the case that psychopharmacologic response patterns might differ among multiple sclerosis patients compared with more general psychiatric patients. The results indicate a modest but favorable response of the treated subjects to desipramine, as measured by clinical judgment and Hamilton depression scores but not as measured by Beck scores.

Side effects from medication were more common in the desipramine group, and half of the desipramine patients could not be brought above the 125 ng/ml serum level, which was the dosing target. Nonetheless, the same percentage of these patients improved ($N=6$ of 7) as in the group whose serum levels exceeded 125 ng/ml (6 of 7). This finding may indicate that the desipramine therapeutic window of 125–200 ng/ml does not rigorously apply to depressed patients with this particular neuroimmunologic disease. The blood-brain barrier is known to be interrupted in multiple sclerosis, and it is possible that the distribution kinetics for drug into the CNS are different in this population.

It is also of interest that only a weak correlation existed between severity of depression and severity of neurologic disease, as measured by Kurtzke Expanded Disability Status Scale scores. This finding may cast doubt upon the hypothesis that depression in multiple sclerosis patients is a psychological response to lost function, or it may at least indicate that such psychological processing is more complex than may have been suspected. In addition, it seems clear that depression improved equally among patients across the spectrum of neurologic disability. This observation, at least from a psychiatric perspective, argues against therapeutic nihilism with respect to the severely disabled.

There was a divergence in the results of this study concerning improvement in depressive symptoms on the measures of depressive severity. We designed our study in advance with blind, functionally based clinical judgment as our primary outcome measure, and a significant change occurred on this measure. This result was corroborated by the significant improvement in Hamilton depression scores experienced by the desipramine group. Improvement on the Beck scores did not reach statistical significance for the drug-treated patients, however. There are several possible explanations. First, the magnitude of psychopharmacologic response to antidepressants in these patients was not vastly greater than their response to the standardized psychotherapy, which was given to all subjects. It may be that the additional increment of clinical improvement that is conferred by drug therapy is just not large enough to show up significantly among all dependent variables. Another possibility is that patients tend to underestimate the severity of their depressive disturbance on a self-report scale such as the Beck scale. It is known that multiple sclerosis patients underestimate the presence and severity of their cognitive disturbance, and the same may apply to emotional states.

Many unanswered questions remain with regard to the affective disturbances that occur among people with neuroimmunologic disturbances such as multiple sclerosis. Are there biologic connections that condition the affective disturbances, and if so, are these connections immunologically based? Are there specific neuroanatomic regions of the CNS that are functionally involved in disturbed affective regulation? What forms of psychotherapy are helpful for such patients, and how should they be applied? These and other questions await future investigations.

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Relation of Psychopathology in General Medical Inpatients to Use and Cost of Services

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The authors investigated the relation between psychopathology in medically ill inpatients and use and cost of medical care services. Of 455 medical inpatients, the Medical Inpatient Screening Test identified 27.9% as very depressed, 27.5% as very anxious, 20.2% as having cognitive dysfunction, and 8.6% as having high pain levels. Overall, the test identified 51% of the patients as having high levels of psychopathology or pain. These subjects had a 40% longer median length of hospital stay and 35% greater mean hospital costs than those with low levels of psychopathology or pain. Patients with greater psychopathology also had higher hospital charges, more procedures during hospitalization, and more discharge diagnoses but did not differ from the other patients in sex, race, age, diagnosis-related group (DRG) major diagnostic category, or DRG weight.

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This report focuses on the relation of symptoms of psychopathology and pain to costs of inpatient medical care, especially with respect to length of hospital stay. Previous retrospective studies have demonstrated that medical patients with psychopathology use more medical care services than patients without psychopathology (1–4), but few prospective studies, particularly of medical inpatients, have been reported (5). The relation between comorbid psychopathology and hospital costs is of particular interest in light of the cost offset, i.e., whether mental health care interventions reduce medical care expenditures. Using a screening instrument for anxiety, depression, confusion, and pain in general medical inpatients, we prospectively studied the relation between the presence of psychopathology and utilization of medical care. This study was the first phase of a randomized controlled study of psychiatric consultation.

METHOD

The potential subjects were all consecutively admitted to general medical services at the Medical College of Virginia Hospital between July 1, 1987, and Feb. 5, 1988. Patients were not considered for the study if they became unavailable because of early discharge, transfer, or death. For patients with multiple admissions during the study period, only the first hospitalization was included. Of 678 patients considered for the study, 223 were excluded. Patients were excluded if they did not speak English (N=3), were judged by the nursing staff to be too physically ill to undergo a brief interview (N=85), or were judged by the screeners to be unwilling (N=53) or unable (N=82) to give informed consent. Four hundred fifty-five patients met the inclusion criteria and entered the study after giving written informed consent.

Patients were approached during the first 24–48 hours after admission and asked to participate in a study of the "psychological effects of physical illness." After agreeing to participate, subjects were given the Medical Inpatient Screening Test (6), a composite instrument measuring anxiety, depression, confusion, and pain. Anxiety and depression were assessed by using the 23 questions from the Hopkins Symptom Checklist (SCL-90-R) (7, 8) that measure these two symptoms. The cutoff scores and their rationale have been described previously (6).

Cognitive dysfunction was identified with the Mini-Mental State examination (9). Patients who scored 21 or less out of a possible total score of 30 were considered to have significant cognitive dysfunction. Pain was measured by using visual analogue scales of sensory intensity and affective magnitude (10). These scales consisted of 15-cm lines whose end points were designated as "no sensation" and "the most intense sensation imaginable" for the sensation scale and as "not bad at all" and "the most intense bad feeling possible for me" for the affect scale. Scores were measured in centimeters from a low of 0 to a high of 15. For this study the two pain scale scores were summed;

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TABLE 1. Demographic and Utilization of Care Variables for 678 Medical Inpatients Included and Not Included in a Study of Psychopathology and Costs of Care

	Patients Included in Study (N=455)				Patients Excluded From Study (N=223)				
Variable	N	%	Mean	SD	N	%	Mean	SD	Analysis
Sex									χ^2=2.23, df=1, n.s.
Male	229	50.4	—	—	125	56.6	—	—	
Female	225	49.6	—	—	96	43.4	—	—	
Race									χ^2=1.71, df=1, n.s.
White	141	31.2	—	—	57	26.3	—	—	
Black	311	68.8	—	—	160	73.7	—	—	
Primary payer									χ^2=56.8, df=2, p<0.0001
Medicaid (or patient was indigent)	205	47.2	—	—	67	31.2	—	—	
Medicare	130	30.0	—	—	129	60.0	—	—	
Blue Cross or private insurance	99	22.8	—	—	19	8.8	—	—	
Age (years)	—	—	49.2	16.2	—	—	61.8	18.1	t=9.12, df=673, p<0.0001
Length of hospital stay (days)	—	—	10.1^a	12.2	—	—	18.7^b	24.9	z=7.00, p<0.0001^c
DRG^d weight	—	—	1.20	0.72	—	—	1.42	1.04	z=3.65, p<0.0003^c
Number of discharge diagnoses	—	—	5.82	3.09	—	—	7.69	2.97	z=7.17, p<0.0001^c
Number of procedures	—	—	2.20	2.20	—	—	2.72	2.32	z=3.06, p<0.002^c
Total hospital costs ($)	—	—	6,658	9,153	—	—	10,915	15,661	z=5.38, p<0.0001^c
Total hospital charges ($)	—	—	8,998	13,405	—	—	15,454	22,995	z=5.88, p<0.0001^c

[a] Median=6 days; range=1–143 days.
[b] Median=10 days; range=1–182 days.
[c] Wilcoxon rank sum test.
[d] Diagnosis-related group.

a combined score greater than 24 (maximum score=30) was chosen as identifying patients with a high degree of pain. In a pilot sample, 11% of the patients were above the pain cutoff score (6). Administration of the Medical Inpatient Screening Test battery took approximately 20 minutes per patient.

Data on demographics, discharge diagnoses, diagnosis-related group (DRG), length of hospital stay, number of procedures, and total costs and charges for the index hospitalization were obtained for each subject from the hospital's computerized records after the patient's discharge. Costs were estimated by the hospital by means of a standard ratio-of-cost-to-charges method based on the Medicare cost report.

As a measure of severity of medical illness, we chose DRG weights, which are used by the Medicare prospective payment system as an approximate indicator of resource use and disease severity across DRG categories. While DRG weights have acknowledged limitations, they serve as the current adjustors for reimbursement. DRG weights thus seemed most appropriate for examining the relation between comorbid psychopathology and utilization of services. Other available measures of disease severity also have limited established validity.

The demographic and utilization variables for the study subjects and the patients who were excluded are shown in table 1. Since patients were systematically excluded if they were too ill to be interviewed or too demented to give informed consent, the excluded patients, as anticipated, were significantly older and had longer hospital stays, greater DRG weights, more discharge diagnoses, more procedures, and greater hospital costs and charges. They were also more likely to be Medicare patients than to be in other payer categories.

Because many of the variables appeared to be not normally distributed, even after log transformation, nonparametric tests were used for most of the data analyses. For those few analyses for which no nonparametric statistical techniques were available, normal-theory linear model analyses were applied to variables log transformed to the best approximation to normality.

RESULTS

The Medical Inpatient Screening Test identified 27.5% (N=125) of the patients as very anxious, 27.9% (N=127) as very depressed, 20.2% (N=92) as having cognitive dysfunction, and 8.6% (N=39) as having high pain levels. The screen as a whole identified 51% (N=232) of the patient sample as having a high degree of psychopathology or pain (less than the sum of the individual dimensions because of overlap of symptoms). As in our pilot experience (6), men and women were about equally represented among those identified as having a high degree of psychopathology.

The substantial overlap between dimensions of the screening test derives from the relationship of depression, anxiety, and pain. Depression and anxiety fre-

TABLE 2. Demographic and Utilization of Care Variables for 455 Medical Inpatients With High and Low Levels of Psychopathology[a]

	Patients With High Levels of Psychopathology (N=232)				Patients With Low Levels of Psychopathology (N=223)				
Variable	N	%	Mean	SD	N	%	Mean	SD	Analysis
Sex									$\chi^2=0.001$, df=1, n.s.
Male	117	50.4	—	—	112	50.5	—	—	
Female	115	49.6	—	—	110	49.5	—	—	
Race									$\chi^2=0.02$, df=1, n.s.
White	71	30.9	—	—	70	31.5	—	—	
Black	159	69.1	—	—	152	68.5	—	—	
Primary payer									$\chi^2=9.44$, df=2, p<0.009
Medicaid (or patient was indigent)	117	53.4	—	—	88	40.9	—	—	
Medicare	64	29.2	—	—	66	30.7	—	—	
Blue Cross or private insurance	38	17.4	—	—	61	28.4	—	—	
Age (years)	—	—	49.2	16.3	—	—	49.2	16.2	t=0.01, df=452, n.s.
Length of hospital stay (days)	—	—	11.5[b]	12.4	—	—	8.7[c]	11.9	z=3.39, p<0.0007[d]
DRG[e] weight	—	—	1.18	0.63	—	—	1.22	0.80	z=0.96, n.s.[d]
Number of discharge diagnoses	—	—	6.26	3.19	—	—	5.36	2.92	z=3.04, p<0.002[d]
Number of psychiatric discharge diagnoses	—	—	0.50	0.83	—	—	0.34	0.70	z=2.41, p<0.02[d]
Number of procedures	—	—	2.46[f]	2.32	—	—	1.91[g]	2.03	z=2.40, p<0.02[d]
Total hospital costs ($)	—	—	7,634	10,484	—	—	5,643	7,411	z=2.98, p<0.003[d]
Total hospital charges ($)	—	—	10,258	15,511	—	—	7,686	10,666	z=2.86, p<0.004[d]

[a] According to the Medical Inpatient Screening Test.
[b] Median=7 days; range=1–107 days.
[c] Median=5 days; range=1–143 days.
[d] Wilcoxon rank sum test.
[e] Diagnosis-related group.
[f] Median=2; range=0–9.
[g] Median=1; range=0–10.

quently occurred in the same patient. Sixty-seven percent (N=84) of the anxious patients had marked depression, and 66% (N=84) of the depressed patients had marked anxiety (Spearman rank order correlation, $r_s=0.71$, N=454, p<0.0001). Half of the patients with high pain scores had high levels of depression and/or anxiety. Of the patients with high levels of pain, 41% (N=16) had marked anxiety, and 36% (N=14) had high levels of depression. There was no significant overlap or correlation between cognitive dysfunction and the other dimensions of the screening test.

Table 2 gives data on the subjects with high levels of psychopathology or pain and those scoring below the cutoff points. There were no significant differences in sex, race, or age. There were too many different DRGs represented to make meaningful comparisons of specific DRG distributions in the two groups. However, 20 of the DRG major diagnostic categories were represented in the sample, with no difference in distribution between the groups with high and low ratings of psychopathology or pain. Furthermore, DRG weight, which serves as an indicator of disease severity and resource use for each DRG, did not differ between the two groups. Patients with high degrees of psychopathology had significantly longer hospital stays, more procedures during hospitalization, and higher total costs and charges. Patients with high psychopathology or pain levels also had a higher total number of discharge diagnoses and more psychiatric discharge diagnoses than those without high levels. The difference in total number of discharge diagnoses was mostly attributable to medical (not psychiatric) diagnoses, which accounted for over 80% of the difference. When only the subjects with high levels of depression, anxiety, or cognitive dysfunction (i.e., excluding subjects with high levels of pain alone) were compared to the subjects with low levels, the differences in length of stay, costs, charges, procedures, and diagnoses remained equally significant.

As expected, length of stay was closely correlated with total cost of hospitalization ($r_s=0.92$, N=676, p<0.0001) and DRG weight ($r_s=0.43$, N=675, p<0.0001). Length of stay was also modestly correlated with depression (r=0.11, N=454, p<0.02), cognitive dysfunction (r=0.14, N=455, p<0.003), and pain (r=0.13, N=452, p<0.006). (These p values may be more reflective of the large sample size than of the magnitude of the correlations.) Patients in each of the four subcategories of the Medical Inpatient Screening Test had median hospital stays greater than those of patients who scored below the cutoffs (table 3).

Patients with high levels of psychopathology or pain were more likely to receive Medicaid or be indigent than to possess Blue Cross/Blue Shield or private insurance. Medicare patients were equally represented in both groups. To assess the extent to which a difference in length of stay between patients with high and low levels of psychopathology or pain might be due to

TABLE 3. Length of Hospital Stay of 455 Medical Inpatients Grouped According to Level of Psychopathology or Pain[a]

Group	Length of Stay (days)				Analysis[b]
	Mean	SD	Median	Range	
Low level of psychopathology (N=223)	8.8	0.8	5	—	—
High level of psychopathology					
Depressed (N=127)	11.1	11.1	6	2–63	$z=2.43$, $p<0.01$
Anxious (N=125)	10.7	11.0	6	2–63	$z=2.26$, $p<0.02$
Cognitive dysfunction (N=92)	11.7	11.2	7	1–56	$z=2.86$, $p<0.004$
High level of pain (N=39)	17.9	20.2	10.5	2–107	$z=4.21$, $p<0.0001$

[a] According to the Medical Inpatient Screening Test.
[b] Wilcoxon rank sum test.

payer status, we examined the relation between rating on the Medical Inpatient Screening Test and log transformed length of stay after partialing out payer status. The log transformation was used because of the abnormal distribution of length of stay. In this normal-theory linear model, there was no significant main effect of payer status on log length of stay ($r=2.24$, $df=2, 430$, $p<0.10$), suggesting that payer status is not an important determinant of differences in length of stay. This ANOVA model accounted for comparatively little of the variation in log length of stay (about 4%), but three-fourths of that (about 3%) was attributable to rating on the screening test, even after we controlled for payer status.

DISCUSSION

To our knowledge, this is the first prospective study of the effect of symptoms of depression, anxiety, cognitive dysfunction, and pain on utilization of inpatient medical care. We found that the presence of comorbid psychopathology was associated with an increase in utilization of medical care. Patients with high levels of psychopathology had a 40% longer median stay (7 versus 5 days) and 35% greater mean costs than patients with low levels of psychopathology. The group with greater psychopathology also underwent more procedures while in the hospital, a further contribution to costs in addition to that of the longer stay.

The finding that comorbid psychopathology was associated with greater use of medical care would be a trivial one if the patients with more psychopathology (higher scores on the screening test) had been more medically ill than the patients with lower levels of psychopathology. Since chronic medical conditions are themselves associated with a greater risk of psychopathology (11), it is possible that the greater utilization occurs in a population who are *medically* sicker and have psychopathology as a consequence, not a cause. This explanation of the findings is unlikely, since the groups with higher and lower scores on psychopathology or pain did not differ in the distribution of DRG major diagnostic categories. Furthermore, the two groups did not differ in DRG weights, suggesting that the patients were comparably distributed in terms of disease severity. Thus, the greater utilization of medical care that we found to be associated with more psychopathology or pain symptoms does not appear attributable to a difference in severity or type of medical illness.

Previous studies demonstrating higher utilization of medical inpatient services associated with comorbid psychopathology have mainly been retrospective ones, which are limited by their focus on psychopathology recognized *and* recorded by nonpsychiatric physicians and their failure to control for severity of medical disease in most cases. Both of these flaws are limitations of the studies by Fulop et al. (2) and Dvoredsky and Cooley (12). Using medical diagnoses from discharge summaries, Fulop et al. demonstrated that hospital stay was significantly longer for medical patients with psychiatric diagnoses than for those without such diagnoses in large samples drawn from two teaching hospitals (19.8 versus 9.2 days at one; 13.7 versus 8.3 days at the other). Dvoredsky and Cooley also used medical discharge diagnoses and found longer stays for Veterans Administration hospital patients who had medical and psychiatric diagnoses than for those who had only medical diagnoses.

Other retrospective studies have compared utilization by patients who received psychiatric consultation with utilization by those who did not. Like the discharge diagnosis studies we have mentioned, these consultation studies were also limited by their focus on a small recognized subset of patients and by failure to control for severity of medical disease. Using a national sample that included 263,000 patients at 327 hospitals, Wallen et al. (1) found that medical patients who received psychiatric consultations (less than 1% of the total number of patients) had a longer mean stay (16.3 days) than all other medical-surgical patients (7.3 days). Hales et al. (13) compared patients who received a psychiatric consultation for organic brain syndrome to all other patients and found that they had six times the length of stay, but these investigators did not control for demographic variables or severity of illness as we did in this study. An additional limitation in interpreting uncontrolled, nonrandomized studies of the relation between psychiatric consultation and length of hospital stay is that consultations of all types are associated with greater length of stay (14).

Prospective studies of utilization by inpatients who have both medical illness and psychopathology have been fewer but have also not controlled for severity of physical illness. P.L. Jenkins et al. (unpublished manuscript, 1990) studied a general surgical population and found that results on the General Health Questionnaire did not influence length of stay. Thomas et al. (5) focused on the effects of delirium in general medical patients and found that the mean stay of those with delirium was 10 days longer than that of the patients without delirium, although they noted that the two groups were not comparable with respect to specific medical diagnoses.

Better controlled studies of the impact of medical-psychiatric comorbidity have focused on outpatients. Wells et al. (15) recently reported from the Medical Outcomes Study that depressive symptoms had an independent additive effect on the physical and social functioning of patients with chronic medical illness.

In contrast with earlier studies that failed to do so, we examined demographic variables. The high- and low-psychopathology groups in our study did not differ in age, race, or sex. Patients with high levels of psychopathology were more likely to be indigent or on Medicaid and less likely to have Blue Cross or private insurance. The greater length of stay and resource use that we found for patients with greater psychopathology are unlikely to be attributable to their being indigent or on Medicaid for two reasons. First, a recent study of 65,032 patients at 52 Boston hospitals (16) found that after adjustment for DRG and the presence of mental illness as a second diagnosis, indigent patients had *shorter* hospital stays than Blue Cross patients. There was no difference in length of stay between Medicaid and Blue Cross patients. Second, our data analysis indicated that payer status did not seem to be an important determinant of length of stay and did not explain most of the difference in length of stay attributed to high level of psychopathology (high score on the Medical Inpatient Screening Test).

In this study patients with high levels of psychopathology had more diagnoses than those with low levels of psychopathology. This is consistent with previous research which demonstrated that patients with mental disorders both utilize more medical care services and receive care for more diagnostic categories than other patients (17, 18).

We identified 51% of our patient population as having high levels of psychopathology, comparable to the results of other studies measuring psychopathologic symptoms in the medically ill (19–21, and unpublished paper by P.L. Jenkins et al., 1990). Direct comparison of studies is difficult because of differences in the symptoms examined, the screening instruments used, and the target patient populations. The General Health Questionnaire has identified 45%–61% of general medical inpatients as having emotional dysfunction (19, 20), 37% of general surgical patients (Jenkins et al.), and 43% of neurology inpatients (21).

About 28% of our sample was identified as depressed, which is within Katon's estimated prevalence range of 20%–33% (22), based on a variety of instruments, cutoff scores, and inpatient samples. Previous studies have found significant depressive symptoms in 24%–34% of medical inpatients according to the Beck Depression Inventory (19, 23, 24), 33.5% according to the Center for Epidemiologic Studies Depression Scale (25), and 34.5% according to structured interviews (26).

We identified 20% of the patients in our study as having significant cognitive dysfunction according to the Mini-Mental State examination, slightly less than the previously reported rates of 25%–30% (19, 27, 28). The true rate in our hospital is likely higher, since we excluded patients who were incapable of giving informed consent, most of whom had severe organic brain symptoms.

This study was limited to selected psychopathologic symptoms and did not use standardized psychiatric diagnoses. This design was derived from our need for a simple, brief screening instrument that would be well tolerated by medical inpatients and their physicians and nurses. Thus, our results for depression, for example, apply to depressive symptoms rather than depressive disorder. This may not limit generalizability, since Wells et al. (15) found in the Medical Outcomes Study that depressive symptoms, with or without depressive disorder, were associated with poor functioning in patients with eight chronic medical conditions.

Our results are limited to the patients we included in the study, which represented two-thirds of those eligible. Most of the remainder were excluded because they were too ill for a brief interview or were unable to give informed consent. The absence of knowledge about the psychopathology and medical care utilization of the excluded subjects does not reduce the relevance of our findings. The greater utilization of medical care that is associated with psychopathology can be targeted for reduction through experimental psychiatric interventions. Psychiatric intervention is more difficult with medical patients who are too ill to be interviewed or unable to give informed consent. Thus, our findings apply to those patients for whom psychiatric intervention is potentially more practicable.

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Panic Disorder and Cardiovascular/Cerebrovascular Problems: Results From a Community Survey

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Follow-up studies of psychiatric patients with panic disorder have shown an abnormally high mortality rate in men due to cardiovascular and cerebrovascular events. The authors report that in the New Haven portion of the Epidemiologic Catchment Area program the risk for stroke in persons with lifetime diagnoses of panic disorder was over twice that in persons with other psychiatric disorders or no psychiatric disorder. After adjustments for demographic differences between groups, the risk was even higher. While the results should be interpreted cautiously because of the small sample and absence of medical examinations, these findings are consistent with clinical studies showing an association between panic disorder and cardiovascular/cerebrovascular events.

(Am J Psychiatry 1990; 147:1504–1508)

Panic disorder includes recurrent episodes of sudden and unpredictable apprehension and is associated with such symptoms as dyspnea, palpitations, chest pain, choking, and sweating. Because these symptoms mimic several medical conditions, patients with panic disorder are high users of medical services (1). While an association between panic disorder and cerebrovascular problems has been noted, psychiatric assessments of patients with panic symptoms attending cardiology clinics have suggested that the association may stem from improper differential diagnosis due to the overlap between symptoms of panic and angina or cardiac arrhythmia (2–7). Other investigators have suggested that the above-normal frequency of mitral valve prolapse and possible accompanying arrhythmias in patients with panic disorder may explain a real association (7, 8).

For example, an above-normal risk of strokes and transient ischemic attacks in women less than 45 years old who have mitral valve prolapse has been shown (9, 10). However, all investigators are not in agreement about the association between panic disorder and mitral valve prolapse (11). One study showed that panic disorder is unusually common in patients with idiopathic dilated cardiomyopathy who are undergoing evaluation for cardiac transplant (12); other findings suggest mild left ventricle hypertrophy or dilation in panic patients (13). Coryell et al. (14, 15) showed a high mortality rate in men due to cardiovascular or cerebrovascular disease or to suicide in a 35-year follow-up of inpatients with panic disorder. This finding was replicated, although weakly, in two shorter, independently conducted follow-up studies of outpatients (16, 17). The greater likelihood of cardiovascular or cerebrovascular control mechanisms in panic disorder has been under investigation (18). For example, Taylor et al. (19), studying autonomic dysfunction, noted that patients with panic disorder have higher submaximal exercise treadmill heart rates, mean daily heart rates, and sleep heart rates than do control subjects.

ECG monitoring of panic attacks showed the high rates to be sinus tachycardia (20). Similarly, many studies not directly involving panic disorder have shown an association between mental stress and myocardial ischemia (21). Haines et al. (22), in a 6-year follow-up study of 1,457 white men 40 to 64 years of age who lived in northwest London, found that initial high scores for phobic anxiety were strongly related to subsequent major ischemic heart disease (fatal and nonfatal events combined) even when other associated variables (preexisting myocardial infarction at recruitment, cholesterol concentration, measured hemostatic variables, blood pressure, smoking, and age) were controlled. It is interesting that phobic anxiety was associated with fatal ischemic heart disease but not death from other causes.

All of the studies except the Haines study have included patients coming for treatment to cardiac, psychiatric, or primary care clinics. Because of the tendency for persons with more than one disorder to come for treatment, a selection bias may exaggerate the association between panic disorder and cardiovascular or cerebrovascular problems. Epidemiologic

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studies that include probability samples of the community may overcome the selection bias of patients coming for treatment but are weakened by the absence of clinical detail. In this paper we examine the relationship between reports of selected cardiovascular and cerebrovascular problems and diagnoses of panic disorder in a probability sample of community residents. Since the actual number of persons with both panic disorder and the medical conditions under study is small, the results must be interpreted with caution; however, they are of interest in light of their consistency with findings from clinical studies.

METHOD

Epidemiologic Catchment Area (ECA) Program

The ECA program is an epidemiologic study of rates and risks for psychiatric disorders based on a random sample of over 18,000 adults aged 18 and over living in five U.S. communities (New Haven, Conn.; St. Louis; Baltimore; Durham, N.C.; and Los Angeles). A full description of the purpose, methods, and sampling frame of the ECA study can be found elsewhere (23).

Each ECA program site used the NIMH Diagnostic Interview Schedule (DIS) (24), a highly structured interview designed for epidemiologic studies that generates *DSM-III* diagnoses for the major psychiatric disorders. Each site included some questions that were not part of the core battery. In New Haven, respondents were asked if they ever had hardening of the arteries, high blood pressure, a heart attack, or a stroke. No attempt was made to query respondents about mitral valve prolapse. Only the New Haven data are presented here. This sample was drawn from 13 towns in the New Haven, Conn., standard metropolitan statistical area; 5,034 persons were interviewed, including an oversample of about 2,500 persons 65 years of age and older.

Psychiatric Groups

The total sample was divided into three groups. The first group included each subject with a diagnosis of panic disorder at some time in his or her life. They may also have had other psychiatric disorders. The second group included each subject with a positive (lifetime) diagnosis of any of the following *DSM-III* disorders: major depression, dysthymia, bipolar disorder, obsessive-compulsive disorder, somatization disorder, alcohol or drug abuse, and antisocial personality disorder. These constitute the majority of adult axis I disorders in *DSM-III*. Subjects in this second group never had panic disorder. The third group comprised individuals without lifetime panic disorder and without any of the major psychiatric diagnoses just listed. The numbers of subjects in the tables vary slightly from the full sample because of missing data.

Data Analyses

Our cross-tabulations presenting rates of disorder by sociodemographic variables include actual numbers of persons surveyed and their weighted percent in the sample. Each sample subject has a known probability of selection from the target population. The weight is assigned to each respondent to compensate for under- or oversampling when determining population prevalence (23).

We analyzed the statistical associations between the four cardiovascular/cerebrovascular outcome variables and the three diagnostic groups using the cross-tabulations with raw percents and by means of logistic regression. The following demographic characteristics in the logistic regressions were controlled: age (as a continuous variable); sex; socioeconomic status, as a continuous variable represented by a composite score for education, income, and occupation; race (white or nonwhite); and marital status (married, single, separated/divorced, or widowed).

Adjusted odds ratios with 95% and 99% confidence intervals were derived from the logistic regressions (25). Adjusted odds ratios provide an index of the strength of the associations between the diagnostic groups and the cardiovascular or cerebrovascular outcomes while controlling for key variables. Statistical significance of the odds ratio can be judged by whether or not the confidence interval excludes 1. An odds ratio with a confidence interval including 1 indicates no abnormally high risk. An odds ratio that has a confidence interval with a lower limit greater than 1 indicates a significantly higher than normal risk.

RESULTS

Characteristics of the Sample

A total of 60 New Haven subjects had lifetime panic disorder, representing a weighted mean of 1.5%. An additional 1,036 had other psychiatric disorders, which represents a weighted mean of about 26.1%. Over 3,700 subjects (weighted mean of 72.4%) never had any psychiatric disorder.

There were significant differences on all of the demographic variables between the diagnostic groups (table 1). All five sociodemographic factors were controlled in subsequent multivariate analyses, as described in the Method section.

Association With Cardiovascular/Cerebrovascular Problems

Table 2 shows the raw frequencies of the cardiovascular and cerebrovascular problems in the three psychiatric diagnostic groups. According to the chi-square statistic, only stroke approached statistical significance ($\chi^2=4.73$, df=2, p=0.09) across the three groups. In

TABLE 1. Sociodemographic Characteristics of Subjects With Lifetime Diagnoses of Panic Disorder, Other Psychiatric Disorders, or No Psychiatric Disorder in the New Haven ECA Site

	Panic Disorder (N=60, weighted %=1.5%)		Other Psychiatric Disorder (N=1,036, weighted %=26.1%)		No Psychiatric Disorder (N=3,778, weighted %=72.4%)		Chi-Square Analysis		
Characteristic	N	Weighted %	N	Weighted %	N	Weighted %	χ^2	df	p
Sex							19.03	2	0.001
Male	12	21	467	51	1,517	45			
Female	48	79	570	49	2,261	55			
Age (years)							312.22	8	0.001
18–24	5	7	146	21	266	15			
25–34	22	36	261	32	450	19			
35–44	15	29	140	17	327	15			
45–64	11	25	165	23	614	33			
65 and over	7	2	325	8	2,121	19			
Marital status							180.06	6	0.001
Married	25	55	471	52	1,930	63			
Widowed	6	5	157	4	1,000	9			
Divorced/separated	19	28	182	15	307	7			
Single	10	12	227	29	539	20			
Socioeconomic status (quartile)							23.72	6	0.001
Bottom	4	4	112	6	602	10			
Second	22	43	403	36	1,356	33			
Third	18	28	343	39	1,166	36			
Top	16	25	176	19	643	22			
Race							18.67	4	0.001
White	54	90	885	84	3,370	87			
Black	5	9	95	11	313	10			
Other	1	1	48	5	86	3			

TABLE 2. Prevalence of Self-Reported Cardiovascular/Cerebrovascular Problems in Subjects With Lifetime Diagnoses of Panic Disorder, Other Psychiatric Disorders, or No Psychiatric Disorder in the New Haven ECA Site

	Prevalence (weighted %)		
Health Problem	Panic Disorder (N=60)	Other Psychiatric Disorder (N=1,036)	No Psychiatric Disorder (N=3,778)
Hardening of the arteries	1.7	7.6	7.0
High blood pressure	26.7	30.8	28.8
Heart attack	8.3	8.6	7.3
Stroke[a]	8.3	3.5	3.3

[a] Significant difference between subjects with panic disorder and those with no psychiatric disorder (χ^2=5.95, df=1, p=0.05); the difference approached significance for the comparison of all three groups (χ^2=4.73, df=2, p=0.09) and for panic disorder versus other psychiatric disorders (χ^2=3.73, df=1, p=0.06).

unadjusted comparisons, the subjects with panic disorder had a risk of stroke over twice as high as that for subjects with other psychiatric disorders (χ^2=3.73, df=1, p=0.06) or no psychiatric disorder (χ^2=5.95, df=1, p=0.05).

When demographic characteristics were controlled (table 3), the results of the logistic regressions showed that subjects with panic disorder were at higher risk of having high blood pressure (adjusted odds ratio=1.91), heart attack (adjusted odds ratio=4.54), and stroke (adjusted odds ratio=11.95) than the group with no psychiatric disorder. Compared to subjects with no psychiatric disorder, those with psychiatric disorders other than panic were at higher risk of having hardening of the arteries (adjusted odds ratio=2.15), high blood pressure (adjusted odds ratio=1.77), heart attack (adjusted odds ratio=2.08), and stroke (adjusted odds ratio=1.69). The comparisons between the subjects with panic disorder and the subjects with any other psychiatric disorder yielded significant results for stroke only (adjusted odds ratio=7.09) (table 3).

The higher risk seen in the adjusted analyses reflects the younger overall age of the panic disorder group (table 1). We cautiously interpret the higher risk as suggesting that if the relatively young panic group were as old as the no-disorder and other-disorder groups, the differences seen in table 2 would be even greater. The adjusted analyses in table 3 merely assure that the associations reported in table 2 were not due to confounding demographic variables.

DISCUSSION

The limitations of the study are obvious. Medical examinations and laboratory tests were not conducted. While the sample surveyed was large, the actual number of people with both stroke and panic disorder was small. On the other hand, the use of a probability sample overcomes the selection bias of a clinic sample.

Viewed within these limitations, these findings are

TABLE 3. Adjusted Odds Ratios for Cardiovascular/Cerebrovascular Problems in Subjects With Lifetime Diagnoses of Panic Disorder, Other Psychiatric Disorders, or No Psychiatric Disorder in the New Haven ECA Site

Comparison	Adjusted Odds Ratio[a]	95% Confidence Interval[b]	p
Hardening of the arteries			
Panic versus other disorder	2.27	0.06–3.45	n.s.
Panic versus no disorder	1.05	0.12–7.30	n.s.
Other versus no disorder	2.15	1.61–2.87	0.001
High blood pressure			
Panic versus other disorder	1.07	0.58–1.99	n.s.
Panic versus no disorder	1.91	1.04–3.51	0.04
Other versus no disorder	1.77	1.50–2.10	0.001
Heart attack			
Panic versus other disorder	2.18	0.80–5.99	n.s.
Panic versus no disorder	4.54	1.67–12.34	0.003
Other versus no disorder	2.08	1.58–2.73	0.001
Stroke			
Panic versus other disorder	7.09	2.44–20.63	0.001
Panic versus no disorder	11.95	4.22–33.84	0.001
Other versus no disorder	1.69	1.12–2.53	0.01

[a] Adjusted for age, sex, marital status, race, and socioeconomic status.

[b] A confidence interval with a lower limit greater than 1.00 indicates above-normal risk.

interesting when considered against the Coryell et al. and Martin et al. mortality studies and the Haines et al. follow-up study. Coryell et al. (16), in a 12-year follow-up of 155 outpatients with anxiety, noted that the high rate of deaths ascribed to cardiovascular or cerebrovascular disorders on death certificates for men was due to a variety of terminal events. In a 35-year follow-up of 113 former inpatients with panic disorder, Coryell et al. (15) found a high rate of mortality for men due to cardiovascular or cerebrovascular disease. Martin et al. (17) studied 500 outpatients in a 7-year follow-up. Sixty percent of the patients had panic disorders. A significant association between cardiovascular or cerebrovascular mortality and panic disorder was found. The Haines et al. (22) longitudinal study of men 40 to 64 years of age showed that initial high scores for phobic anxiety were associated with a high risk of fatal ischemic heart disease 6 years later, even when other associated risk factors were controlled. The relationship between high levels of phobic anxiety and *DSM-III* panic disorder is unclear.

Our findings raise questions about possible mechanisms to explain the association. The two major mechanisms for stroke are thromboembolism (loosening of a blood clot from the heart or carotid artery) and hemorrhage (usually the rupture of an artery in the brain during a hypertensive episode). Thromboembolic strokes are more common. A relationship to panic disorder could be mediated by panic-related enlargement of the left ventricle of the heart (12). Left ventricle enlargement increases the risk of thrombus formation and subsequent risk of stroke. Alternatively, if panic disorder increases the risk of hypertension (not strongly supported here), there could be a consequent risk of hemorrhagic strokes. It is also possible the association is due to stroke-induced brain damage and consequent panic disorder. The relatively early onset of panic (range, 8–35 years) in our sample makes this unlikely. The association observed may be due to an indirect increase in risk factors. Persons with panic disorder may be less prudent in their diets, drinking, smoking, or other health habits. For example, in one study (26) a significantly higher than expected number of patients with panic disorder had cholesterol values that exceeded the 75th percentile of national reference values for their age and sex.

The association between the presence of any psychiatric disorders, high blood pressure, and heart attacks is of interest since others have shown an association between mental stress and myocardial ischemia, independent of physical exertion (21). Clinical studies are required to replicate the findings and to determine possible mechanisms.

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Successful Treatment of Nonpurging Bulimia Nervosa With Desipramine: A Double-Blind, Placebo-Controlled Study

Una D. McCann, M.D., and W. Stewart Agras, M.D.

Twenty-three women with nonpurging bulimia underwent a 12-week, double-blind, placebo-controlled trial of desipramine hydrochloride. Repeated standardized rating scales, mood assessments, and self-reports of dietary habits were used to measure changes in binge frequency and cognitive processes associated with food intake. The women who received desipramine reduced their frequency of binge eating by 63%, but women receiving placebo increased their frequency of binge eating by 16%. Twelve weeks after initiating treatment, 60% of the treatment group but only 15% of the placebo group abstained from binge eating. The women who received desipramine showed significantly more dietary restraint and reported significantly less hunger, suggesting that desipramine acts to suppress appetite. These preliminary findings suggest that the therapeutic effects of desipramine established in the treatment of purging bulimia nervosa extend to patients with nonpurging bulimia.

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There is a subpopulation of patients with bulimia nervosa who engage in regular binge eating without purging (1–4). Typically, these patients have a history of numerous strict or fad diets, punctuated by recurrent episodes of binge eating. Like patients with purging bulimia, patients with nonpurging bulimia have persistent overconcern with body shape and weight. Unlike patients with purging bulimia, patients with nonpurging bulimia tend to be overweight and, by definition, continue to binge without purging by means of self-induced vomiting or laxative use. Binge episodes are typically terminated because of the need for sleep, social interruptions, or abdominal pain.

Surprisingly, this subpopulation of patients with bulimia has not been included in previous controlled medication trials for the treatment of bulimia (5–15). This is unfortunate, since effective treatments for nonpurging bulimia are needed because of the health risks associated with bulimia and with obesity (e.g., hypertension, hypercholesterolemia, diabetes, and degenerative joint disease) (16). The exact prevalence of nonpurging bulimia is not known but is likely to be substantial. An estimated 20% to 46% of overweight adults seeking treatment for weight loss engage in regular binge eating without purging (2, 4, 17). Given that 34 million adults in the United States are overweight (16), even if only a small fraction of these met the full criteria for bulimia nervosa, it would represent a large number of individuals.

Antidepressant medications have been found to be quite useful in the treatment of patients with purging bulimia (5–15). Although they have not been uniformly successful, the rate of reported treatment success, defined as abstinence from binge and purge behaviors, has been as high as 68%. When defined as reduced binge eating, the success rate reported has been as high as 91%. The purpose of this study was to determine whether desipramine hydrochloride is also effective in the treatment of nonpurging bulimia. The relationship between the purging and nonpurging forms of bulimia and binge eating in nonbulimic individuals is not known. However, since the symptom of binge eating characteristically responds to antidepressant treatment to a greater degree than does the symptom of purging (16–21; *DSM-III-R*), we hypothesized that patients with nonpurging bulimia might also be treated effectively with antidepressant medications. To evaluate this hypothesis, a double-blind, placebo-controlled trial was undertaken testing the efficacy of desipramine hydrochloride in the treatment of women with nonpurging bulimia.

METHOD

Women with nonpurging bulimia were recruited by a behavioral medicine clinic through notices in local newspapers, newsletters, and a local television health program. The women were required to have an average of at least two binge eating episodes per week for a minimum of 1 year and to meet the *DSM-III-R* requirements for bulimia nervosa. As such, they all had

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TABLE 1. Past and Present *DSM-III-R* Diagnoses of 30 Women With Nonpurging Bulimia

Diagnosis	Number	Percent
Purging bulimia nervosa	1	3
Current major depression	3	10
Past major depression	15	50
Past substance abuse	7	23
Current panic disorder	1	3
Past panic disorder	3	10
Present generalized anxiety	1	3
Past generalized anxiety	1	3
Present social phobia	4	13
Past social phobia	4	13
Present simple phobia	6	20
Past simple phobia	7	23
Agoraphobia	1	3

histories of strict dieting or fasting and persistent overconcern with their body weight and shape. The women were required to keep a food diary for the week before the study in order to verify historical self-reports of binge eating. All of the women considered themselves at least 15% overweight, although body mass indices (weight in kg divided by height in meters squared) ranged from the upper limits of normal (body mass index=23) to morbidly obese (body mass index=41). All of the women underwent a standardized interview for *DSM-III-R* diagnoses (the Structured Clinical Interview for DSM-III-R) (22) (see table 1). Excluded from the study were women who regularly purged (either by vomiting or laxative abuse), were taking psychotropic medications, or suffered from a psychotic condition or current drug abuse. The women were required to have medical clearance from an internist before their participation in the study, and all provided written, informed consent. The women were randomly allocated to either desipramine or placebo.

The women were seen at the clinic for the first 4 study weeks and then at weeks 6, 9, and 12. A follow-up visit was conducted at week 16. Sessions were conducted by a study psychiatrist (U.D.M.) unaware of the medication condition, using a standard protocol. Specific questions were asked regarding the number of binge episodes during the previous week, number of days in the previous week during which binge eating occurred, adherence to the medication, medication side effects, and depression. Due to the nature of binge eating not clearly terminated by a purging episode, the women with nonpurging bulimia were able to recall the number of days on which binge eating occurred better than they could recall the total number of binges per day. Therefore, the number of days of binge eating per week was felt to be a more accurate measure of binge frequency.

The women kept food diaries during the week before the medication trial, during the 12th week of the trial, and during the 4th week following discontinuation of medication. This method of assessment was kept to a minimum because food diaries are often used as a therapeutic intervention in cognitive and behavioral therapies for eating disorders (23). They could, therefore, add another variable to the study. The women were counseled on how to cope with medication side effects and, if necessary, how to maximize compliance. Counseling regarding diet, weight loss, and psychological concerns was specifically avoided. Each session lasted approximately 15 minutes.

An initial dose of 25 mg/day of desipramine hydrochloride (one capsule) was prescribed on the first week of the study. Medication was gradually increased, depending on therapeutic response and tolerance of side effects, to a maximum of 300 mg/day. The women were instructed to increase their dose by one capsule (25 mg) every 2 days for the first week. Capsules containing 50 mg were used during the second week, and, again, the women were told to increase their medication dose by one capsule (50 mg) every 2 days, unless they were unable to tolerate the side effects, in which case they were told to continue to take their maximum tolerated dose. At each clinic visit, the women were required to bring their medication bottle, and all pills were counted and accounted for. During week 12, medication was discontinued by slow taper over a 7–10-day period.

The average dose of desipramine taken was 188 mg/day (range=100–300 mg/day). The average dose of placebo was five capsules (range=3–6 capsules).

Seven of the women dropped out during the course of the drug trial. Two of these were receiving placebo, and five were receiving active medication. Of the latter, two withdrew at week 3 after developing drug-associated skin eruptions, two dropped out because of a feeling of malaise (week 2 and week 9), and the fifth failed to keep her second appointment (week 2), stating that she would be unable to participate in the study because of scheduling conflicts. In the placebo group, one patient withdrew from the study at week 9 because of unpleasant feelings in her throat, and another failed to keep follow-up appointments following her first visit.

In addition to the data collected by the study psychiatrist during clinic visits, the women were weighed and asked to complete a computerized battery of questionnaires on weeks 0, 3, 6, 9, 12, and 16. Questionnaires included the Beck Depression Inventory (24), the Three-Factor Eating Questionnaire (25), the Semantic Differential Scale (26), and the Bulimic Thoughts Scale (unpublished 1986 paper of D.L. Franko et al.). The Beck inventory was designed to assess depressive symptoms. The Three-Factor Eating Questionnaire is composed of three subscales: cognitive restraint (restraint), tendency toward disinhibition of eating (disinhibition), and perceived hunger (hunger). The Semantic Differential Scale provides a measure of body image. The Bulimic Thoughts Scale provides an assessment of dietary cognitions associated with binge eating.

Data were analyzed by using a repeated-measures analysis of covariance, with the baseline value of the measure as the covariate.

TABLE 2. Outcome Measures in 23 Women With Nonpurging Bulimia Before and After a 12-Week Trial of Desipramine (N=10) or Placebo (N=13)

	Women Given Desipramine		Women Given Placebo	
Measure	Mean	SD	Mean	SD
Days of binge eating per week[a]				
Before treatment	3.8	1.8	2.5	1.9
After treatment	1.4	2.2	2.9	2.3
Binges per week[b]				
Before treatment	3.8	1.8	3.5	2.6
After treatment	1.4	2.2	3.7	3.4
Disinhibition score on the Three-Factor Eating Questionnaire[c]				
Before treatment	13.7	1.5	13.3	2.0
After treatment	7.5	4.5	13.1	1.7
Hunger score on the Three-Factor Eating Questionnaire[d]				
Before treatment	10.6	3.1	8.2	4.2
After treatment	6.0	3.7	8.8	3.6
Restraint score on the Three-Factor Eating Questionnaire[e]				
Before treatment	8.2	5.2	9.5	2.4
After treatment	12.4	4.7	9.6	4.8
Bulimic Thoughts Questionnaire score				
Before treatment	41.2	11.2	42.6	13.4
After treatment	36.9	9.6	46.8	16.5
Body image score on the Semantic Differential Scale				
Before treatment	3.1	0.8	3.4	0.8
After treatment	4.1	1.1	3.8	1.0
Beck Depression Inventory score				
Before treatment	12.4	6.9	12.1	8.7
After treatment	6.4	7.1	7.7	6.5
Weight (kg)				
Before treatment	91.6	20.1	89.1	16.0
After treatment	88.1	18.9	87.9	14.9
Body mass index				
Before treatment	31.7	4.7	30.3	5.0
After treatment	30.6	4.1	29.9	4.8

[a] The difference between groups was significant ($F=9.2$, $df=1, 22$, $p<0.006$).

[b] The difference between groups was significant ($F=4.63$, $df=1, 22$, $p<0.04$).

[c] The difference between groups was significant ($F=17.5$, $df=1, 21$, $p<0.001$).

[d] The difference between groups was significant ($F=8.81$, $df=1, 21$, $p<0.007$).

[e] The difference between groups was significant ($F=4.62$, $df=1, 21$, $p<0.04$).

RESULTS

After 12 weeks of treatment, the women receiving desipramine decreased the number of days per week that they engaged in binge eating by 63%, but the women receiving placebo showed a 16% increase (see table 2). Similarly, although the medication group showed a decrease of 63% in total number of binges per week, this behavior increased by 6% in the placebo group (see table 2). Sixty percent (N=6) of the treatment group and 15% (N=2) of the placebo group abstained from binge eating at the 12-week assessment.

In terms of secondary measures, the medication group had a significantly greater reduction in the tendency for disruptive environmental events to precipitate binge eating than the placebo group (the disinhibition subscale) (see table 2). The medication group also reported a significantly greater reduction in hunger (the hunger subscale) and a significantly greater increase in dietary restraint (the restraint subscale) than the placebo group (see table 2). There were no significant differences between groups in the remaining secondary measures, including bulimic thoughts, perception of body image, depression, and weight (see table 2).

As shown in figure 1, when medication was discontinued there was a tendency for disinhibition, hunger, and binge eating frequency to return to baseline by the 16-week assessment, although this tendency did not reach statistical significance.

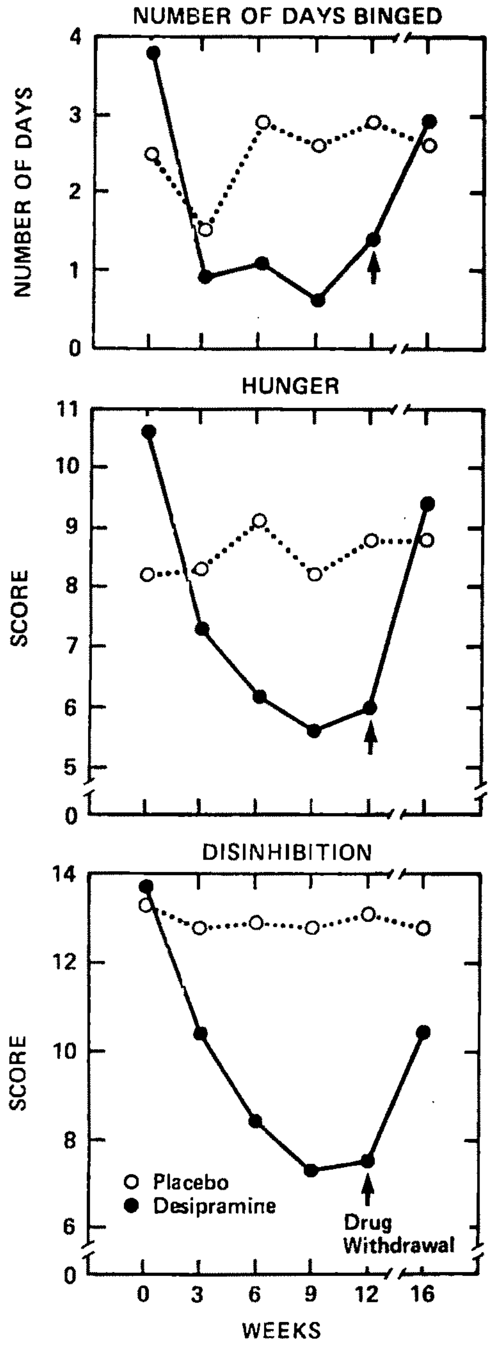
DISCUSSION

The present findings suggest that desipramine may be useful in the treatment of nonpurging bulimic patients. Desipramine, given over a 12-week period, resulted in a 63% reduction in the frequency of binge eating in women with nonpurging bulimia, but placebo administration was associated with a 16% increase in binge frequency. In addition, desipramine led to a total abstention from binge eating in 60% of women over 12 weeks, whereas only 15% of the placebo group was abstinent at 12 weeks. These observations suggest that desipramine, previously found to be successful in the treatment of purging bulimia, is also useful in the nonpurging form of this disorder.

The present results also suggest that the antidepressant action of desipramine is not essential for its efficacy in reducing binge eating, since the participants in this study had low scores on the Beck inventory and were not clinically depressed. Moreover, there were no significant differences in depression between groups following treatment. Although arguing against the hypothesis that bulimia nervosa is an expression of major depression, this finding still leaves open the possibility that bulimia nervosa shares the same chemical mechanism as major depression. Thus, reductions in binge eating brought about by desipramine could be secondary to the same neurochemical mechanisms that bring about improvements in depressive symptoms (27, 28).

Although previous studies have identified an increase in dietary restraint as a key factor in promoting binge eating (3), our findings indicate that it is not the sole factor in precipitating bulimia. Although the women in this study had high scores at baseline on the restraint subscale of the Three-Factor Eating Questionnaire, desipramine treatment was associated with an

FIGURE 1. Frequency of Binge Eating, Perceived Hunger, and Ability of Environmental Events to Precipitate Binge Eating (Disinhibition) in 23 Women With Nonpurging Bulimia During and After a 12-Week Trial of Desipramine (N=10) or Placebo (N=13)



increase rather than a decrease in dietary restraint. Taken alone, these results would seem to be at odds with those of other investigators, which would predict an increase rather than a decrease in binge eating with increased dietary restraint (3). However, the two findings can be reconciled if one assumes that in addition to dietary restraint, a heightened sense of hunger is needed to promote binge eating. Thus, although the women had a greater tendency to restrict food intake and a heightened perception of hunger at baseline, treatment with desipramine significantly reduced their perception of hunger and therefore reduced their binge eating. This interpretation, if correct, would suggest that the primary action of desipramine on binge eating is through appetite suppression and that reducing hunger facilitates the patient's efforts to resist environmental factors that precipitate binge eating. Others have found desipramine to have appetite-suppressant effects (27) and to enhance the anorexigenic actions of amphetamine (28).

As a group, the women receiving desipramine lost an average of 3.5 kg; the weight loss in some individuals was dramatic (15.9 kg). Although the mean difference in weight loss between the placebo and medication groups did not achieve statistical significance, it is important to emphasize that no dietary counseling was offered (to avoid confounding the effects of desipramine) and that the women were told that reduction of binge eating rather than weight reduction was the chief aim of the study. The absence of dietary counseling and structured cognitive or behavioral methods typically used in weight loss programs could possibly also account for the failure of scores on the bulimic thoughts questionnaire to change in conjunction with the decrease in binge eating.

Although the results of this study are encouraging, they should be regarded as preliminary. The number of subjects who completed the medication trial is small (23 of 30 women). However, the fact that there was a significant difference between the two groups in spite of this small number of subjects suggests that the treatment effects may actually be quite robust. It should also be noted that several of the women who received desipramine developed side effects (rash, orthostatic hypotension, generalized malaise). Such side effects could limit the patient population that can be effectively treated with desipramine. The clinical utility of desipramine in the treatment of binge eating may also be limited by the tendency for subjects to resume binge eating following withdrawal from desipramine. This finding suggests that the anti-binge-eating effects of desipramine are short-lived, at least when taken only for a 12-week period, and that recidivism following discontinuation of medication may be a problem. Longer medication trials or different dose regimens need to be tested to determine whether more permanent improvements in eating patterns and greater patient compliance are attainable with desipramine. More lasting effects might also be achieved if desipramine therapy was used as one component of a structured behavioral weight reduction program.

In summary, the results of this study suggest that desipramine is superior to placebo in the treatment of nonpurging bulimia nervosa. Further, they suggest that antidepressants may exert their therapeutic action in bulimia by suppressing appetite rather than by elevating mood. Additional clinical trials addressing both the pharmacological and cognitive aspects of bulimia may help in efforts toward devising more effective and specific treatments for patients who suffer from this common eating disorder.

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Update on the Epidemiology of Anorexia Nervosa in a Defined Region of Switzerland

Jürg Willi, M.D., Graziella Giacometti, M.D., and Bernhard Limacher, Ph.D.

In this follow-up investigation, the authors studied all Swiss women in the canton of Zurich who developed anorexia nervosa between ages 12 and 25 years and who were hospitalized for the first time with this diagnosis between 1983 and 1985. Data were compared with those from an earlier study, which focused on the periods 1956–1958, 1963–1965, and 1973–1975. The incidence of anorexia nervosa did not increase significantly during 1983–1985 compared to 1973–1975, in contrast to the constant increase found between 1956 and 1975. However, the more frequent use of vomiting and abuse of laxatives in 1983–1985 may indicate an increase in cases with mixed features of anorexia nervosa and bulimia.

(Am J Psychiatry 1990; 147:1514–1517)

In 1983 we published a study in the *American Journal of Psychiatry* (1) on the incidence of hospitalizations of women for anorexia nervosa in the canton of Zurich during three randomly selected sampling periods between 1956 and 1975. The data were gathered retrospectively from case histories on file at all pediatric, medical, and psychiatric clinics in the canton. We found an overall significant increase in the incidence of anorexia nervosa, from 0.38 cases/100,000 for 1956–1958 to 0.55/100,000 for 1963–1965 to 1.12/100,000 for 1973–1975. Age at onset of illness, interval between onset and first hospitalization, and illness profile remained constant across all three periods. With the present study we add a further sample drawn 10 years later (1983–1985).

METHOD

The canton of Zurich, one of 25 Swiss cantons, represents a clearly defined region that included approximately 1,120,000 inhabitants in the period 1983–1985 (1,035,666 in 1970). The canton is highly industrialized and is served by a supraregional university hospital and an extensive network of central and regional hospitals. The cost of treatment is fully covered by health insurance. Because fees for treatment outside the canton are higher, it is unlikely that anorexic patients from the canton of Zurich would be hospitalized elsewhere.

All private and state clinics of internal medicine, pediatrics, and psychiatry in the canton of Zurich were surveyed in our study; they included 28 medical clinics or departments, four pediatric clinics or departments, one clinic for child psychiatry, seven psychiatric clinics, and two psychotherapeutic clinics. We had access to all archives of the included hospitals. Since the files for more recent years are now computerized at all hospitals, it was—contrary to the situation in 1975—not difficult to locate the registered cases. In the earlier investigations, data were missing from six smaller private hospitals because of insufficient records. These hospitals were included in the present study. Because only one case could be identified in these hospitals for the period 1983–1985, the error in relation to the 1973–1975 study is not significant.

All medical records indicating anorexia nervosa were examined. When medical information was missing or incomplete, doctors or patients were contacted by telephone and questioned. We did not attempt to study the incidence of bulimia, since the medical record entries are still unreliable in this regard and many patients tend to deny these symptoms when questioned over the telephone.

We included all Swiss women residing in the canton of Zurich who developed anorexia nervosa between the ages of 12 and 25 and who were hospitalized in a Zurich hospital because of anorexia nervosa for the first time in their lives during 1983–1985. The clinical diagnosis of anorexia nervosa had to be unambiguous, i.e., other psychiatric or somatic illnesses had to be ruled out. Only patients whose weight at admission was at least 15% under normal weight (according to Geigy tables [2]) and at least 25% below the subject's maximum weight before the onset of illness were considered. For patients 15 years old and younger, we used the age-standardized normal-weight tables for Swiss children from birth to 20 years (3).

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TABLE 1. Incidence of Anorexia Nervosa Among Women in the Canton of Zurich and Interval Between Onset and First Hospitalization

Age at Onset (years)	1956–1958 and 1963–1965			1973–1975			1983–1985		
		Interval (years)			Interval (years)			Interval (years)	
	N	Mean	SD	N	Mean	SD	N	Mean	SD
12–15	10	3.0	4.9	13	1.5	1.5	22	2.1	3.6
16–18[a]	10	1.0[b]	1.5	14	3.9[b]	3.1	12	1.0	1.1
19–25	7	2.6	3.0	11	2.5	2.0	14	4.0	3.7

[a] F=7.50, df=2, 33, p=0.002.

[b] Groups significantly different at the 0.001 level; Duncan's test for post hoc differences.

RESULTS

Incidence of Anorexia Nervosa and Demographic Characteristics

Incidence. The incidence of anorexia nervosa during 1956–1958 and 1963–1965, 1973–1975, and 1983–1985 is presented in table 1. For the period 1983–1985, 48 cases of anorexia nervosa were found: 19 for 1983, 12 for 1984, and 17 for 1985. In absolute terms, this represents a clear increase over the three previous periods. The incidence in the total canton population in 1983–1985 was—at 1.43/100,000—higher than in 1973–1975, but this difference is not statistically significant. Furthermore, despite the larger absolute number of cases in 1983–1985, no difference could be found with 1973–1975 in the ratio of anorexic patients to the number of females 12–25 years old in the total canton population. This points to the importance of controlling for the size of the risk group when making such comparisons.

Between 1956 and 1973 we found a shift in the place of first hospitalization from pediatric and internal medicine clinics and departments toward psychiatric clinics and departments. In the 1956–1958 sample, no subject was hospitalized in a psychiatric clinic, while 50% (N=5 of 10 subjects) were hospitalized in pediatric clinics and 50% in internal medicine clinics. In 1963–1965, 6% (N=1 of 17) of the subjects were hospitalized in psychiatric clinics and only 24% (N=4) in pediatric clinics. In 1973–1975, 32% (N=12 of 38) of the subjects were hospitalized in psychiatric clinics, somewhat more than in pediatric clinics. In 1983–1985, psychiatric clinics were—with 35% (N=17 of 48) of first hospitalizations—equal to internal medicine clinics, while pediatric clinics—with 30% (N=14)—ranked somewhat lower. The shift toward psychiatric hospitalization of anorexic patients has thus slowed, possibly as a result of the increase in liaison psychiatry at medical and pediatric clinics over the last 10 years.

Age. The mean±SD age at onset of anorexia nervosa was 16.8±3.2 years, and the average interval between onset and first hospitalization was 2.4 years. Both of these values are consistent with those found for the three previous periods.

Education. In the literature (4, 5), it has been suggested that patients with anorexia nervosa rank above average in intelligence, differentiation in character or sensitiveness, and talent. However, to our knowledge, with the exception of our previous study (1), this has never been statistically investigated and confirmed. The percentage of anorexic patients attending the higher schools (*Sekundarschule* and *Gymnasium*) declined slightly from 1956–1958 (90%; N=9 of 10) to 1973–1975 (84%; N=32 of 38) and significantly from 1973–1975 to 1983–1985 (67%; N=32 of 48) (χ^2=3.36, df=1, p≤0.05). For the 1983–1985 sample, there was no longer a significant difference between the anorexic patients and the total canton population in the type of school attended. This was in contrast to the 1963–1965 and 1973–1975 samples, for which the difference between anorexic patients and the total population at the seventh school year (1966–1967) was highly significant (χ^2=7.23, df=1, p≤0.01, and χ^2=12.53, df=1, p≤0.001, respectively).

Socioeconomic status. We categorized the fathers (age range, 40–59 years) of the anorexic patients into five socioeconomic classes. Fifty percent (N=5 of 10) of the fathers were assigned to the higher classes I–III for the period 1956–1958, 71% (N=12 of 17) for 1963–1965, 74% (N=28 of 38) for 1973–1975, and 79% (N=38 of 48) for 1983–1985. These figures differ sharply from those for the total population, of which only 28% fell into these categories in 1970 and 1980. Our investigation revealed a decrease in the school performance of the anorexic patients but an increase in the occupational status of their fathers.

The Anorexia Nervosa Syndrome

The illness profile has remained constant regarding age at onset and interval between onset and first hospitalization.

Weight loss. The body weight at the time of first hospitalization was compared to normal weight (average weight by sex, age, and height [2, 3]). In order to be defined as anorexic, a patient had to have lost—through refusal of food—at least 25% of her maximum weight before onset of illness and had to be at least 15% below normal body weight. These criteria are in accordance with the definition adopted by Feighner et al. (6) and with *DSM-III*, both of which require a loss of at least 25% of original body weight.

For the 1983–1985 sample, the mean deviation from normal weight was 17.9±5.0 kg, i.e., 32.8%; this represented a significant increase in the mean weight loss over the four samples (1956–1958: 25.5%; 1963–1965: 28.4%, 1973–1975: 30.6%) (F=3.35, df=3, 109, p≤0.05). A pre-illness deviation of more than 5 kg from normal weight was found in 51% (N=33 of 65) of the patients in the first three samples (30% [N=20] were overweight, 20% [N=13] were underweight). For the 1983–1985 period, on the other hand, the figure was 71% (47% [N=23 of 48] were overweight, 23% [N=11] were underweight). More of the patients included in the last sample, then, deviated from normal weight and were overweight than were patients in the earlier samples.

Menstruation. The age at first menstruation remained constant across all four time samples, with a mean of 13.1 years for 1956–1958 (range=12–15), 12.9 years for 1963–1965 (range=11–19) and 1973–1975 (range=10–16), and 12.8 years for 1983–1985 (range=11–17). At the time of hospital admission, only four of the 48 subjects in the 1983–1985 sample reported normal menstruation; 37 had amenorrhea, and five had not yet begun to menstruate. In addition, there was one case of oligomenorrhea and one case of earlier amenorrhea treated with oral contraceptives.

Vomiting and abuse of laxatives. Vomiting was reported for 75% (N=36 of 48) of the subjects in the 1983–1985 sample; this figure was significantly larger than those for the three previous samples (approximately 50% for each: N=5 of 10 for 1956–1958, N=9 of 17 for 1963–1965, and N=17 of 38 for 1973–1975) (χ^2=8.53, df=1, p≤0.01). Similarly, the abuse of laxatives was significantly more often reported in the 1983–1985 sample (in 50% of the subjects [N=24 of 48], compared to approximately 30% in the three previous periods: N=1 of 10 for 1956–1958, N=5 of 17 for 1963–1965, and N=14 of 38 for 1973–1975) (χ^2=4.29, df=1, p≤0.05). Since information relating to vomiting and abuse of laxatives is probably not very reliable, it had to be supplemented —as in the earlier survey—through questioning of patients and doctors.

DISCUSSION

The results of our study can hardly be compared with those of other investigations, since certain factors of sample selection have often been given little attention. An epidemiological study of anorexia nervosa should be based on consideration of the following three methodological criteria.

1. Definition of cases: for identification as a case of anorexia nervosa, we required a weight loss of at least 25% of the pre-illness maximum weight (according to *DSM-III*) *and* at least 15% of the normal weight (according to *DSM-III-R*) for age, sex, and body size (according to Geigy tables [2]). Our study shows that the pre-illness weight was not identical with the expected normal weight: in 71% (N=34 of 48) of the subjects in the 1983–1985 sample, the pre-illness weight deviated more than 5 kg from the expected normal weight.

2. Definition of age at onset of illness: the incidence as a proportion of the total canton population showed a slight, nonsignificant increase for the 1983–1985 sample; however, the incidence as a proportion of the same-age risk group showed no such increase. The same-age risk group has, until now, received very little attention in the literature.

3. Definition of case registration: an increase in the number of cases at psychiatric institutions (7, 8) is to be expected simply for the reason that, as was found in the present study, the proportion of first hospitalizations in psychiatric institutions has increased over the last 30 years, while the relative number of cases in pediatric and medical clinics has declined.

Although it is generally assumed that anorexia nervosa has increased in the last several decades, we are aware of only three other studies that used methodological criteria similar to those outlined earlier in this paper. Theander (5) studied the first hospitalization of subjects with anorexia nervosa in medical, gynecological, and psychiatric clinics in a defined region of southern Sweden and found an increase in the number of cases from 1933 to 1960. The studies of Jones et al. (9) and Lucas et al. (10) are not comparable with ours because they included inpatient and outpatient treatment of anorexia nervosa.

Despite an increase in the absolute number of cases of anorexia nervosa in the 1983–1985 sample compared to that of 1973–1975, the incidence has not increased for either the total or the same-age risk group population. The risk group population as a proportion of the total population was nearly 30% larger in the 1983–1985 period than it was in 1973–1975. This can be traced to the large number of births during the early 1960s. In contrast to the earlier decades, then, the incidence of anorexia nervosa has not increased further, a surprising finding.

There has been a progressive trend in the last several years to manage anorexic patients on an outpatient basis whenever possible. Could it be that those who enter hospitals represent only the most severely ill and intractable cases? We have no references to prove that. If we take *all* Swiss women (ages 12 to 25 years) hospitalized for the first time with the *clinical* diagnosis of anorexia nervosa and not only those with a marked weight loss as required in the present study, we have to augment our sample with additional, milder cases, i.e., 1956–1958 by two cases (20%), 1963–1965 by six cases (35%), 1973–1975 by 11 cases (29%), and 1983–1985 by 20 cases (48%). Thus, there was even an increase in milder cases of anorexia nervosa in women who were hospitalized in 1983–1985 compared with 1973–1975.

The profile of the illness has remained more or less constant, particularly with regard to age at onset and interval between onset and hospitalization. Nevertheless, the mean deviation from normal weight has become greater over the decades. Even before the onset of anorexia nervosa, a greater deviation from normal weight—usually toward overweight—was found for the 1983–1985 sample. This may indicate that eating problems more often preceded the onset of the illness.

From 1973–1975 to 1983–1985 there was an increase in the occurrence of vomiting and abuse of laxatives. We found the same increase in the larger sample of all women hospitalized with the clinical diagnosis of anorexia nervosa, including those with a less severe loss of weight. This finding suggests that the number of cases with mixed features of anorexia nervosa and bulimia may have increased.

A further interesting finding relates to education: in the literature it is repeatedly stressed that anorexic patients come from higher socioeconomic strata and display above-average school achievement. This relationship was confirmed for the earlier samples of our study but not for the 1983–1985 period. In the latter sample, fathers of anorexic patients were—as expected—of higher occupational status, but the patients themselves were characterized by school achievement comparable to that of the total canton population. The proportion of upper-level high school pupils among the anorexic patients was considerably smaller in the 1983–1985 sample than in the earlier samples.

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Thyroid Function and Ultrasonically Determined Thyroid Size in Patients Receiving Long-Term Lithium Treatment

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Thyroid function was investigated in 100 manic-depressive patients. Goiter was more common in patients treated with lithium for 1–5 years (44%) or more than 10 years (50%) than in patients who never received lithium (16%). Smoking contributed significantly to thyroid size and goiter. In nonsmoking patients, ultrasonically determined thyroid volume was significantly related to treatment duration. The mechanism behind this increased thyroid volume is unclear, as most patients had normal serum thyrotropin levels and no thyroid autoimmunity. Subclinical or overt hypothyroidism was found in 4% and 21% of patients treated for 1–5 and more than 10 years, respectively. Since few hypothyroid patients had autoimmunity or goiter, lithium may affect the thyroid gland directly.

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Lithium decreases the level of thyroid hormone in serum, while the serum thyrotropin (TSH) level is increased (1, 2). In normal subjects lithium increases thyroid size (2), and in cross-sectional studies of manic-depressive patients receiving lithium therapy the frequency of goiter has varied from 3.6% to 48% (3, 4). Although the serum TSH level rises during the first 12 months of therapy, it usually stays within the normal range (2, 5) and does not rise further as therapy continues (5). One aim of the present study was to investigate the frequency of goiter, precise thyroid size determined ultrasonographically (6), and thyroid function in relation to length of treatment and signs of thyroid autoimmunity in a large group of manic-depressive patients treated with lithium for up to 22 years.

It has been reported that the prevalence of high serum TSH levels (subclinical or overt hypothyroidism) increases in relation to increasing length of lithium treatment (7–9). This long-term effect of lithium is found mainly in female patients and has been attributed to induction of thyroid autoimmunity (7, 10), although this possibility has been questioned by others (11), since lithium does not seem to induce autoantibody production *de novo*. The suggestion that lithium has a toxic effect on the thyroid gland (12) is supported by the extensive fibrotic changes found by histopathological investigations of thyroid glands from patients treated with lithium (13). A further aim of the present study was to look for a relation between thyroid autoimmunity, hypothyroidism, and thyroid size and thereby give indirect evidence that lithium can induce Hashimoto's thyroiditis or atrophic thyroiditis.

METHOD

One hundred manic-depressive patients attending a hospital outpatient psychiatry clinic were invited to participate in a study on thyroid function. All gave informed consent. The psychiatric diagnoses were made according to the *International Classification of Diseases*, 8th ed (*ICD-8*). The patients were given lithium treatment only after at least three psychotic episodes (manic or depressive) over a period of 2 years. We divided the patients into three groups on the basis of length of lithium treatment.

The first group contained 19 patients (11 women) who had never been treated with lithium. These patients were used as a comparison group. Their median age was 46 years (range, 22–65 years). Nine had bipolar disease, seven had unipolar disease, and three had agitated reactive psychosis.

The second group contained 25 patients (15 women) who had been treated with lithium for 1–5 years (median, 3 years). Their median age was 46 years (range, 25–65 years). Seventeen had bipolar disease, seven had unipolar disease, and one had an agitated reactive psychosis.

The third group contained 56 patients (42 women) who had been treated with lithium for more than 10 years (median, 18; range, 11–22 years). Their median age was 55 years (range, 35–71 years). Thirty-six had bipolar disease, and 20 had unipolar disease. Six of these 56 patients had been given levothyroxine for hy-

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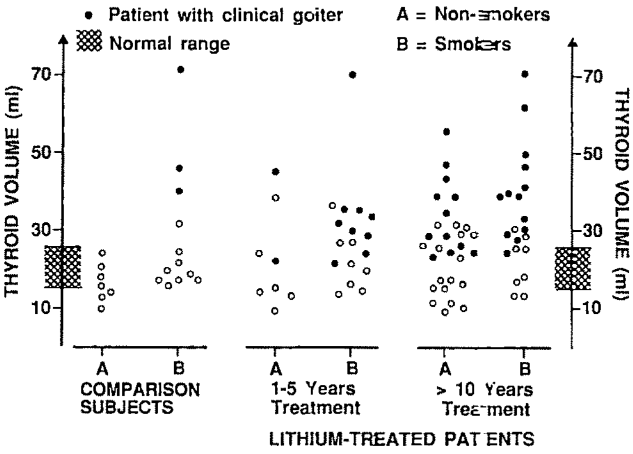
pothyroidism for more than 1 year. This diagnosis was based on prior clinical and biochemical evidence of hypothyroidism. These patients were not included in the study of thyroid volume, goiter prevalence, serum TSH, and response to thyrotropin-releasing hormone (TRH).

All patients were asked about other medication, smoking habits, alcohol consumption, and previous and present major disease. Cigarette smoking is probably one of the most important causes of sporadic goiter in our area (14), and the data for smokers (more than five cigarettes daily for more than 5 years) and nonsmokers were analyzed separately. Each patient was asked to give a family history. Two independent observers, both experienced endocrinologists, independently judged whether a goiter was present. Agreement of the two on the presence of a goiter was required for classification of the patient as goitrous.

Levels of serum thyroxine (T_4), triiodothyronine (T_3), T_3 resin uptake, and TSH were determined as previously described (2); the measurement of thyroglobulin antibodies (15) and microsomal antibodies (16) is also described elsewhere. The levels of autoantibodies were considered significantly above normal, thus indicating thyroiditis, if the microsomal antibody level was ++ or above (range, 0 to +++) and the level of thyroglobulin antibodies was 10 mU/liter or above. A TRH test was performed for each subject; the serum TSH level was measured before and 20 minutes after the injection of 200 μg of TRH. This TRH dose has been used in our previous studies (2), and the serum TSH levels found after 20 minutes of TRH stimulation were sufficient to compare the increases in serum TSH concentration in different groups (2). Serum was stored at −20 °C and analyzed in consecutive assays.

The ultrasonic scanning procedure and the total thyroid volume calculation were performed, as previously described (6), with a compound (static images) scanner (type 1846, Brüel and Kjaer, Naerum, Denmark). The transducer was a 5.5-MHz type mechanically focused at 1–3 cm. The scanning procedure, volume calculation accuracy, and precision of the method have all been reported previously (6). In short, with the patient supine, transverse scans of the thyroid were obtained at 5-mm intervals from caudal to cranial with hyperextension of the neck. The outline of the gland on the screen was digitized by tracing it with a cursor (light pencil) connected to a computer; the area within each outline and the volume between two successive transverse scans were then calculated. The sum of all partial volumes equals the total thyroid volume. The precision of the ultrasonic method is between 5.1% and 7.8% in this range of thyroid volume (16) and is expressed as the coefficient of variation on double determinations. The day-to-day variation was of the same magnitude (16). The following formula describes the relationship between thyroid volume (Y, in milliliters), body weight (X_1, in kilograms), and age (X_2, in years): $Y=a+b_1X_1+b_2X_2$ and $Y=1.97+0.21X_1+0.06X_2$ (7). This formula was used with the manic-depressive patients to calculate an expected or "normal" volume.

FIGURE 1. Ultrasonically Determined Thyroid Volume in Manic-Depressive Patients Receiving Long-Term Lithium Treatment or No Lithium[a]



[a]The normal range is the expected thyroid volume calculated from the weight and age of these patients.

The results were analyzed nonparametrically with the Kruskal-Wallis test to compare all three groups. A Mann-Whitney test was used for an a posteriori evaluation. Qualitative data (frequencies) were evaluated with a chi-square test. Correlations were evaluated with Kendall's rank correlation test. A 95% confidence limit was used as significance level.

RESULTS

The goiter frequency was higher in both the group of patients treated with lithium for 1–5 years (11 of 25, 44%) and those treated for more than 10 years (25 of 50, 50%) than in the comparison group (three of 19, 16%) (figure 1) ($\chi^2=8.68$, df=2, $p<0.05$). No difference was found when the median thyroid volumes of the three groups were compared (table 1) (Kruskal-Wallis test, T=3.32, df=2, p=0.19).

All patients with clinical goiters in the comparison group were smokers, and the median thyroid volume of the smokers was higher than that of the nonsmoking group (Mann-Whitney test, Z=2.14, $p<0.05$) (table 1). There was no difference in the median thyroid volume or goiter frequency between the smokers and nonsmokers in the two lithium-treated groups (table 1).

A correlation was found between the number of years the patients had been treated with lithium and the thyroid volume in the nonsmoking patients (Kendall's tau=0.34, N=44, $p<0.03$) but not in the cigarette smokers. No correlation was found between the thyroid volume and the serum levels of total T_4, T_3, T_3 resin uptake, TSH, or TSH 20 minutes after TRH stimulation.

The serum TSH levels did not differ significantly in

TABLE 1. Median Thyroid Volume in Manic-Depressive Patients Receiving Long-Term Lithium Treatment or No Lithium

Group	N	Thyroid Volume (ml)	
		Median	Range
Lithium treatment			
1–5 years	25	27	9–70
Smokers	17	28	13–70
Nonsmokers	8	23	9–45
>10 years	50	29	10–70
Smokers	21	33	10–70
Nonsmokers	29	27[a]	10–55
No lithium	19	24	10–71
Smokers	12	28[b]	16–71
Nonsmokers	7	17	10–24

[a] Significantly different from median for nonsmokers not receiving lithium (Mann-Whitney test, Z=2.2, $p<0.03$).

[b] Significantly different from median for nonsmokers not receiving lithium (Z=2.14, $p<0.05$).

TABLE 2. Serum TSH Level Before and After TRH Injection in Manic-Depressive Patients Receiving Long-Term Lithium Treatment or No Lithium

Group	Serum TSH Level (mU/liter)			
	0 Minutes		20 Minutes	
	Median	Range	Median	Range
Lithium treatment				
1–5 years (N=24)	2.1	0.3–28.8	17.4	4.3–36.8
>10 years (N=50)	1.8	0.3–9.5	14.2	0.6–90.0
No lithium (N=19)	1.5	0.3–9.0	12.3	2.3–35.2

the three groups of patients either before TRH stimulation (Kruskal-Wallis test, T=4.16, df=2, p=0.13) or 20 minutes afterward (T=2.7, df=2, p=0.25) (table 2), regardless of subcategories, i.e., smoker/nonsmoker, male/female, bipolar/unipolar. No differences were found between the groups' total T_4, T_3, or T_3 resin uptake.

Goiter frequency and thyroid volume were similar in men and women within the three groups. There was no relationship between type of psychiatric diagnosis and the presence or absence of a goiter.

Seven of the subjects had serum TSH levels above 5 mU/liter. One was from the comparison group and had no goiter, and one was a patient who had been treated with lithium for 1–5 years. She had a goiter and positive thyroid antibodies, indicating Hashimoto's thyroiditis. The remaining five had received lithium for more than 10 years. Of these, one had a goiter and positive thyroid antibodies and the other four had thyroid volumes ranging from 10 to 28 ml (expected, 17–25 ml).

Hypothyroidism was found in one of the 19 comparison subjects, one of the 25 patients with 1–5 years of lithium treatment, and 12 of the 56 patients treated for more than 10 years ($\chi^2=4.52$, df=2, p=0.11). We further analyzed data for all patients with thyroid volumes less than 15 ml: two of the 19 in the comparison group (11%), four of the 25 treated 1–5 years (13%), and seven of the 50 who had received lithium for more than 10 years (14%) ($\chi^2=0.27$, df=2, p=0.88). None of these patients had a high level of thyroid autoantibodies, a family history of thyroid disease, or a history of excessive alcohol intake.

All of the six who had been given lithium for more than 10 years and were also receiving levothyroxine had smaller thyroid volumes than expected; the median was 11 ml (expected, 21 ml), and the range was 7–18 ml (expected, 20–25 ml). Three of these six patients had high levels of thyroid autoantibodies.

DISCUSSION

Varying goiter frequencies—from 3.6% (3) to 48% (4)—have been reported in manic-depressive patients treated with lithium. In previous studies employing ultrasonic evaluation of thyroid size, we have revealed several factors that influence thyroid size (6, 14, 16–20). However, the most important reason for the reported discrepancies in goiter frequency is probably that thyroid size in other studies has been evaluated by means of palpation, which is known to be inaccurate and irreproducible. Finally, daily iodine intake is also known to influence thyroid size (4, 21). Patients treated with lithium for 1–22 years and the untreated comparison subjects had similar median serum TSH levels before and after TRH stimulation. This finding is in accordance with the results of a prospective study by Maarbjerg et al. (5). It is not clear why thyroid volume increases with increasing length of lithium treatment while serum TSH levels are unaltered. Thyroid cells might become more sensitive to the growth-stimulating effect of TSH during long-term lithium treatment, possibly through changes in the thyroidal iodine metabolism. However, we have no data to substantiate these speculations. Lazarus and Bennie (22) have shown that lithium treatment decreases the iodide-concentrating process in human thyroid glands, but this effect lasts only a few months, after which iodide trapping returns to normal. In a short-term study (2) we demonstrated that thyroid size increases even when the basal serum TSH level increases within the normal range. More frequent blood sampling in a prospective study would be needed to demonstrate whether long-term lithium therapy changes the pattern of TSH release in the individual patient in a way that might explain the stimulation of thyroid growth. It should be stressed that 50% of our patients had no goiter even after 11 to 22 years of lithium treatment, most likely illustrating individual differences in susceptibility.

Hypothyroidism, overt or subclinical, was found in 12 (21%) of our 56 patients with more than 10 years of lithium treatment; most of these 12 were women. This sex difference was also found in previous studies (8). However, more than half of these patients had no signs of autoimmune thyroid disease, very few had a goiter, and the rest had ultrasonically determined thyroid volumes that were smaller than expected. Thus, in susceptible subjects lithium may induce fibrosis and shrinkage of the gland by means of a toxic effect (13). Thyroid gland biopsies could have given additional evidence but were not performed. Alcohol abuse, known to decrease thyroid size (18), was not apparent in these subjects.

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Structured Interviews for Borderline Personality Disorder

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The authors compared three instruments used to diagnose borderline personality disorder—the Diagnostic Interview for Borderline Patients (DIB), the Schedule for Interviewing Borderlines, and the Structured Interview for DSM-III Personality Disorders—in 56 patients with personality disorders. A borderline diagnosis was made according to the DIB in 30%, the Structured Interview for DSM-III Personality Disorders in 48%, and the Schedule for Interviewing Borderlines in 55% of the patients. Diagnostic agreement was only 52%, which has implications for the generalizability of results of validation studies of the borderline diagnosis. Improvement in diagnostic agreement requires modification of current criteria sets and/or the use of dimensional models.

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Borderline personality disorder is commonly diagnosed in clinical settings and has been one of the most studied personality disorders in terms of phenomenology, biological markers, treatment response, family history, and outcome. Unfortunately, however, this diagnosis has not been adequately validated because of inconclusive findings or discordant findings across studies. A major problem is that many criteria sets are available for the diagnosis, such as those of Knight (1), Kernberg (2), Grinker et al. (3), Gunderson and Singer (4), and Spitzer et al. (5).

One solution to this dilemma is to develop operationalized criteria in the form of structured interviews to increase diagnostic reliability from setting to setting. Various semistructured interviews have been developed to correlate with the most widely used criteria sets. These include the Diagnostic Interview for Borderline Patients (DIB) (6), based on Gunderson and Singer's criteria; the Structured Interview for DSM-III Personality Disorders (7), based on the criteria of Spitzer et al.; and the Schedule for Interviewing Borderlines (8), also based on the criteria of Spitzer et al. Each of these instruments has demonstrated good interrater and test-retest reliability (9–14), but the concordance of these interviews has not been evaluated, making it difficult to compare the results of studies using the different measures to establish entry criteria.

Although there have been no studies comparing these structured interviews, there have been studies investigating the diagnostic concordance between patients with borderline personality disorder diagnosed according to Gunderson and Singer's criteria (using the DIB) and those diagnosed according to *DSM-III* criteria (using clinicians' judgments). The degree of agreement has varied in previous studies (14–20), with kappa values ranging from 0.45 to 0.83. One study (21) compared the borderline diagnoses made by using the DIB with those made by using the Personality Disorder Examination (22), a structured interview based on *DSM-III* criteria, and found poor concordance between the two instruments in a sample of 22 patients clinically diagnosed as having borderline personality disorder. Given that the DIB, the Structured Interview for DSM-III Personality Disorders, and the Schedule for Interviewing Borderlines are widely used in studies of borderline personality disorder, the purpose of the present study was to measure the degree of agreement among these three instruments in making a diagnosis of borderline personality disorder.

METHOD

The subjects were 56 male patients 18–65 years old who were consecutively referred from the psychiatric services of a Veterans Administration medical center or another medical center for inclusion in an evaluation program for patients with clinical diagnoses of personality disorders. Patients were excluded from the study if they had major medical illnesses or major *DSM-III* axis I diagnoses of schizophrenia, organic mental disorder, bipolar disorder, or current alcohol or drug dependence. Axis I diagnoses were made by using the Schedule for Affective Disorders and Schizophrenia (SADS) (23). All patients were medication free at the time of the study and gave informed consent to participate.

Each interview was conducted by two raters. A different set of raters conduced each interview for any

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given patient and were blind to data obtained from the other instruments. The interviews were conducted in random order for any given patient, and 2–7 days separated each interview. Interrater reliability (kappa) was high for the diagnosis of borderline personality disorder for each of the three instruments (DIB, −0.79; Structured Interview for DSM-III Personality Disorders, −0.78; Schedule for Interviewing Borderlines, −0.81). Structured Interview for DSM-III Personality Disorders informant interviews were conducted for 44 (79%) of the patients; these patients granted permission for such interviews. Disagreements on final scores or diagnoses derived from any specific instrument were resolved by consensus at a meeting of all members of the rating team supervised by a senior clinician (H.M.K.)

For a categorical diagnosis of borderline personality disorder, patients were required to meet four or more of the eight criteria for borderline personality disorder on the Structured Interview for DSM-III Personality Disorders, score 7 or more on the DIB, or score 23 or more on the summed severity scales of the schedule for borderline personality portion of the Schedule for Interviewing Borderlines. To determine categorical agreement on the overall diagnosis of borderline personality disorder and agreement between subscales common to any two instruments, two-by-two kappa values were computed by using the formula $K=(pOBS-pCHA)/1-pCHA)$, where *pCHA*=chance agreement and *pOBS*=observed agreement. Pearson correlations were made by comparing for each subject the number of criteria met on the Structured Interview for DSM-III Personality Disorders, the DIB scaled score, and the total schedule for borderline personality severity score of the Schedule for Interviewing Borderlines.

RESULTS

The mean age of the patients was 37.7, and all were men. Twenty-seven (48.2%) of the patients were separated or divorced, 18 (32.1%) were currently married, and 11 (19.6%) had never been married. The racial composition reflected the general clinic population: 29 (51.8%) were white, 17 (30.4%) were Hispanic, and 10 (17.9%) were black.

Affective disorders were common in the history of the 56 men in the study group: 24 (42.9%) had a diagnosis of major depressive disorder in remission. Also common were past substance abuse (17 [30.4%] of the patients) and anxiety disorders (12 [21.4%] of the patients). These diagnoses were not significantly more common in the patients with borderline personality disorder as diagnosed by any one of the instruments under study; however, the small sample sizes limited the power of these analyses.

There was significant overlap with other personality disorder diagnoses made by using the Structured Interview for DSM-III Personality Disorders: 46 (82.1%) of the patients had more than one personality disorder. Schizotypal (27 [48.2%] of the patients) and histrionic (27 [48.2%] of the patients) personality disorders were the most common, followed by paranoid (19 [33.9%] of the patients), compulsive (17 [30.4%]), antisocial (nine [16.1%]), and narcissistic (six [10.7%]) personality disorders. Other personality disorders were found in less than 5% of the patients.

The three instruments agreed on the presence or absence of borderline personality disorder in 29 (51.8%) of the patients. Thirty-nine (69.6%) of the patients were diagnosed as having borderline personality disorder by at least one instrument; 24 (42.9%) were diagnosed as having borderline personality disorder by at least two instruments, and 12 (21.4%) were so diagnosed by all three. Seventeen (30.4%) of the patients were not diagnosed as having borderline personality disorder by any of the instruments.

The DIB diagnosed borderline personality disorder in 17 (30.4%) of the patients, the Structured Interview for DSM-III Personality Disorders in 27 (48.2%), and the Schedule for Interviewing Borderlines in 31 (55.4%). Fourteen (82.4%) of the 17 patients diagnosed as having borderline personality disorder by the DIB were also diagnosed as having the disorder by the Structured Interview for DSM-III Personality Disorders, and 22 (81.5%) of the 27 patients diagnosed as having the disorder by the Structured Interview for DSM-III Personality Disorders were so diagnosed by the Schedule for Interviewing Borderlines.

The degree of concordance (kappa) for the diagnosis of borderline personality disorder was 0.50 between the Structured Interview for DSM-III Personality Disorders and the Schedule for Interviewing Borderlines, 0.42 between the DIB and the Structured Interview for DSM-III Personality Disorders, and only 0.18 between the DIB and the Schedule for Interviewing Borderlines. However, if the cutoff for a diagnosis of borderline personality disorder on the DIB was lowered to a score of 6, concordance was improved (for the Structured Interview for DSM-III Personality Disorders and the DIB, 0.47; for the DIB and the Schedule for Interviewing Borderlines, 0.73). Pearson's correlations were $r=0.65$, $df=54$, $p<0.001$ for the Structured Interview for DSM-III Personality Disorders and the DIB, $r=0.53$, $df=54$, $p<0.001$ for the Structured Interview for DSM-III Personality Disorders, and the Schedule for Interviewing Borderlines, and $r=0.49$, $df=54$, $p<0.001$ for the DIB and the Schedule for Interviewing Borderlines. Comparisons of common subscales between the instruments are shown in table 1; there was wide variation in agreement between subscales.

DISCUSSION

With agreement on the presence or absence of borderline personality disorder in only 52% of the patients, diagnostic concordance among these three commonly used instruments is not high enough to generalize easily from studies using any one instrument

TABLE 1. Agreement Between Subscales of Three Measures of Borderline Personality Disorder

Subscale	Agreement Between SCID-PD and DIB		Agreement Between SCID-PD and Schedule for Interviewing Borderlines	
	%	kappa	%	kappa
Impulsivity	82	0.63	70	0.23
Interpersonal relations	55	0.16	59	0.24
Affects	77	0.20	70	0.25
Self-damaging acts	—	—	75	0.53
Anger	—	—	80	0.31
Intolerance of being alone	—	—	80	0.37
Chronic boredom	—	—	86	0.64
Identity disturbance	—	—	52	0.10

to studies using another. Agreement of subscales between instruments was also generally poor, even between the Structured Interview for DSM-III Personality Disorders and the Schedule for Interviewing Borderlines, both based on the criteria of Spitzer et al., which suggests that differences in diagnosis are due not only to differences in criteria but also to variations in the instruments themselves.

Correlations of severity of borderline symptoms among the instruments ranged from 0.49 to 0.65 (all significant values). Although it may be argued that these instruments have better utility as measures of severity on a continuum of psychopathology rather than for making categorical diagnoses, the degree of correlation, even on a dimensional scale, is not sufficient to use these instruments interchangeably.

The concordance between the DIB and the Structured Interview for DSM-III Personality Disorders was less than has been found between the DIB and *DSM-III* criteria in previous studies (14–20). This is in part due to the fact that the present study used operationalized criteria (in the form of the Structured Interview for DSM-III Personality Disorders) rather than clinical judgments as to the presence or absence of criteria to make *DSM-III* diagnoses. A previous study (24) has documented the poor concordance among clinicians in making diagnoses of the personality disorders when structured interviews are not used.

Although previous studies have indicated that the DIB diagnoses as many or more patients as having borderline personality disorder than do *DSM-III* criteria (17–20), in our study far fewer patients were diagnosed as having borderline personality disorder by the DIB than by the *DSM-III*-based Structured Interview for DSM-III Personality Disorders. This may be due in part to the fact that almost all previous studies of the DIB and *DSM-III* have examined inpatients only but ours was a mixed group of inpatients and outpatients. There is evidence from one study (25) that the DIB diagnoses fewer patients as having borderline personality disorder in an outpatient setting than in inpatient settings, where patients are more likely to have overt, florid psychopathology. In fact, in our study group, as noted, a cutoff of 6 rather than 7 on the DIB provided the best concordance with the Structured Interview for DSM-III Personality Disorders and increased its sensitivity. Another important reason for more Structured Interview for DSM-III Personality Disorders diagnoses than DIB diagnoses of borderline personality disorder is the fact the Structured Interview for DSM-III Personality Disorders uses informant interviews. Previous studies of the Structured Interview for DSM-III Personality Disorders (26) have indicated that information given by the informants almost always reveals additional psychopathology in the patients. Finally, the fact that all of the patients in our sample were men may have led to the difference in findings, since previous studies (17–20) have reported on the preponderance of women diagnosed as having borderline personality disorder.

Diagnoses in our group of patients were made with the Structured Interview for DSM-III Personality Disorders according to *DSM-III* (not *DSM-III-R*) because the revised instrument was not available at the time of the study. This should not have influenced the diagnosis of borderline personality disorder in our patients to a significant degree because the *DSM-III-R* changes in this diagnosis are not substantial ("intolerance of being alone" was replaced by "frantic efforts to avoid real or imagined abandonment").

To validate the concept of borderline personality disorder, phenomenology will need to be correlated with external validators such as familial/genetic transmission, psychobiological markers, treatment response, and course of illness. Unfortunately, the present study emphasizes the difficulty in making reliable categorical diagnoses across instruments (and thus defining the population we wish to investigate) and brings into question the validity of broad comparisons across studies conducted to date on borderline personality. For example, one of the major ways in which Gunderson and Singer's criteria for borderline personality disorder differ from those of Spitzer et al. is in the inclusion of psychotic-like phenomena in the former. If DIB criteria are used to select a treatment group, those patients may have a preponderance of psychotic-like traits and may be more likely to respond to neuroleptics than a group of borderline patients selected by the Spitzer/*DSM-III* criteria. Interestingly, two studies that used DIB criteria to select patients for studies of the pharmacological treatment of borderline personality disorder (27, 28) found beneficial effects of antipsychotic medications in these patients. However, because of differences in criteria sets, it is not clear that patients diagnosed as having borderline personality disorder according to *DSM-III* would show similar responses to neuroleptics.

There are several strategies that could be used to deal with the difficulty in making reliable diagnoses across studies with currently available instruments. One strategy would be to narrow our focus by attempting to correlate specific, well-defined psychiatric symptoms with biological markers and/or treatment response. For example, measures of irritability and aggression have been correlated with evidence of central serotonergic dysfunction as measured by the prolactin response to the serotonergic agonist fenfluramine (29). Similarly, measures of schizotypy and impaired neurointegrative functioning have been associated with impaired smooth pursuit eye movements (30). In a study of the effects of various medications on specific symptoms of borderline personality, Cowdry and Gardner (27) found that the monoamine oxidase inhibitor tranylcypromine was most effective in improving mood and impulse control but that carbamazepine was most effective in the treatment of behavioral dyscontrol. Once specific biological treatment markers are established for a particular personality trait or symptom cluster, associated traits can be studied to define the boundaries of discrete psychiatric syndromes. Another strategy to improve precision in diagnosing personality disorders is through the use of family studies of genetic markers. Once genetic markers have been established for axis I disorders such as schizophrenia and affective disorders, detailed studies of family members with the same markers may define a subgroup with a subsyndromal disorder corresponding to borderline personality disorder. Investigators of borderline personality disorder (and personality disorders in general) in different settings need to collaborate on developing reliable sets of criteria based on available external validation studies and to cooperate in constantly testing and refining these criteria.

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Children's PTSD Reactions One Year After a Sniper Attack at Their School

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Fourteen months after a sniper attack at an elementary school, level of exposure to that event remained the primary predictor of ongoing posttraumatic stress reactions in 100 schoolchildren who were followed up. Guilt feelings and knowing the child who was killed were associated with a greater number of symptoms. Grief reactions occurred independent of degree of exposure to the event. The authors discuss the public health implications of these longitudinal findings.

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Systematic research studies (1, 2) have demonstrated the relation between exposure to a traumatic event and the number and persistence of posttraumatic stress symptoms in adults. There are few longitudinal studies of children exposed to traumatic events, but clinical descriptive studies (3, 4) have described the persistence of posttraumatic stress symptoms in children.

In this article we report the first-year follow-up results of a longitudinal study of children exposed to a sniper attack. In February 1984 a sniper opened fire with a semiautomatic weapon and two 12-gauge shotguns on a crowded elementary school playground. He killed one child, wounded one staff member, and injured more than 13 children. We previously demonstrated the overriding importance of degree of exposure to an event in acute posttraumatic stress responses (5). Fourteen months after the sniper attack, we conducted a similar study to investigate the persistence of posttraumatic stress symptoms.

Subsequent to this sniper attack, gunmen have opened fire on elementary schools in different locations across the nation. Within the past year, similar incidents have occurred in Winnetka, Ill., Greenwood, S.C., and Stockton, Calif. This longitudinal study explored the potentially serious and persistent impact of exposure to violence on children.

In the acute-phase study we examined four groups of children: those who had been 1) on the playground and directly exposed to the violence, 2) inside the school, 3) no longer at school or absent that day, and 4) off track (on 3-week vacation from this year-round school). There were no significant differences among these four exposure groups with respect to previous life events as measured by the Coddington Life Events Scale. The initial study demonstrated that acute posttraumatic stress symptoms occur in school-age children within weeks of a life-threatening violent event. Age, sex, and ethnicity did not significantly influence the type or severity of symptomatic response. The greater the exposure, the greater the number of posttraumatic stress symptoms reported. Symptoms of reexperiencing, emotional detachment, and increased states of arousal (jumpiness and sleep disturbance) differentiated exposed from nonexposed children. Identifying the event as an extreme stressor and fear of recurrence were common to children at all levels of exposure to the event. Guilt was infrequently reported but was associated with greater severity of reactions.

METHOD

The 14-month follow-up was conducted by University of California, Los Angeles, crisis team members in nearly every classroom of the school and included children in every grade and at every level of exposure. Children who had graduated to the nearby junior high school were interviewed there. During the classroom consultation, all of the children were engaged in a drawing and storytelling exercise. Certain team members conducted more structured interviews with five to eight children in each classroom. Those interviewed included children who had been initially screened and an additional randomly selected group. Approximately equal numbers of black and Hispanic children were selected.

Approximately 99% of the parents gave permission for their children to be reinterviewed. The number of

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children who had moved out of the school district by the time of the 14-month follow-up was normal for this highly mobile south-central Los Angeles school district. Both directly exposed and unexposed children were among those who had left. Of the original 159 children, 100 were reinterviewed (children remaining in the original school and in the nearby junior high only): 19 who had been on the playground, 21 who had been in the school, 28 who had not been at school that day, and 32 who had been off track. There were no significant differences in the distribution of children across exposure levels on these variables: age, sex, prior acquaintance with the deceased, trauma since the event, death of a significant other, previous trauma, or treatment since the event.

We used the same children's version of the Posttraumatic Stress Disorder (PTSD) Reaction Index that we had used in the initial sampling (5). The index is a PTSD scale patterned after criteria for the disorder as described in *DSM-III*. It inquires about reactions specific to the current traumatic event. It has been used to assess specific posttraumatic stress symptoms after exposure to a broad range of traumatic events. The revised children's version was used for this study at both times.

The total number of symptoms a child reported at the time of the interview was recorded as his or her reaction index score. Empirical comparisons of reaction index scores with independent clinical assessments of severity level of PTSD have established these guidelines: a score of 7–9 indicates a mild level of PTSD, a score of 10–12 suggests a moderate level, and a score greater than 12 indicates a severe level. With these guidelines, correlation of reaction index scores with confirmed clinical cases of PTSD has been reported as 0.95 for adults and 0.91 for children (6).

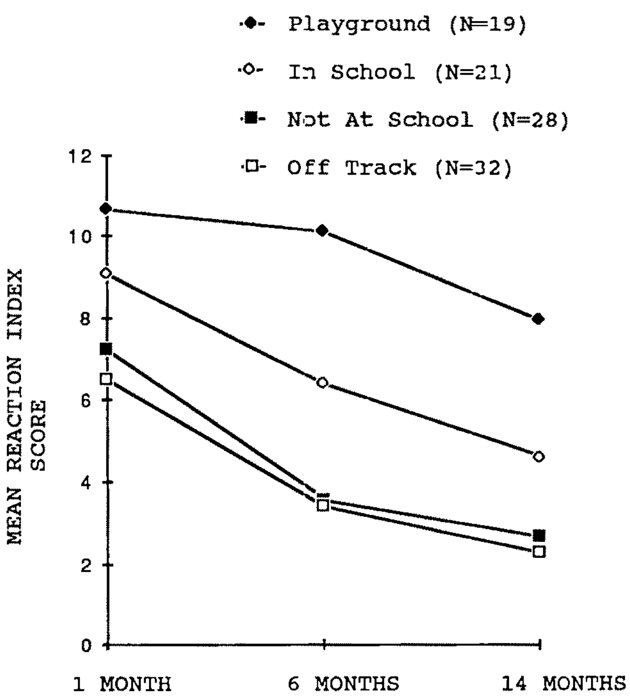
During the 14-month follow-up, children were questioned about their current symptoms and their recollections of symptoms at 6 months. The 14-month date was chosen in order to avoid an exaggeration of symptoms related to the event's anniversary. The specific interval between July 4 and the August 1984 Olympics was used to help the children recall the 6-month point.

Four different interviewers were randomly assigned children from each classroom (5). There were no significant differences between raters in the reaction index scores they gave or in the reaction index scores by exposure level. Interitem agreement for two interviewers who rated the same 10 children was 94%; Cohen's kappa was 0.89.

A brief children's grief inventory was used to examine the relation between the children's grief reactions and their posttraumatic stress reactions. The nine questions and the results of that examination have been published elsewhere (7).

Repeated measures analysis of variance (ANOVA) was used to analyze the continuous data of the reaction index and the grief inventory. We used chi-square analyses to examine the presence or absence of individual symptoms.

FIGURE 1. Mean PTSD Reaction Index Scores Over Time of Schoolchildren With Four Levels of Exposure to a Sniper Attack on the School Playground[a]



[a] "Off track" means on regular 3-week vacation from the year-round school. Significant difference between exposure levels (F=20.6, df=3, 96, $p<0.0001$) and over time (F=55.8, df=2, 192, $p<0.01$).

RESULTS

Trauma prior to the sniper attack, worry about a sibling during the episode, age, sex, and ethnicity were not significantly associated with reaction index scores at the 14-month follow-up. There were significant effects of exposure, time, and having known the deceased victim.

Children who had had greater exposure to the event continued to report more symptoms (figure 1). The results of a repeated measures ANOVA indicated that the number of symptoms was reduced linearly for decreasing levels of exposure and over time. There was not a significant interaction between time and exposure (F=1.5, df=6, 96, $p=0.19$), suggesting that differences between groups were maintained over time. At 14 months, children who had been on the playground during the sniper attack continued to have significantly higher reaction index scores than all other groups (playground children versus children in the school: $t=3.52$, $p=0.0007$; playground children versus children not at school: $t=6.59$, $p<0.0001$; playground children versus children off track: $t=6.96$, $p<0.0001$) (Bonferroni-corrected $p<0.0001$). There were no differences among the other three groups.

Greater initial exposure was associated with significantly greater severity of response at 1 month (Spearman rank-order correlation, $r_s=0.36$, $N=100$, $p<$

TABLE 1. Endorsement of PTSD Reaction Index Items by Schoolchildren After a Sniper Attack on the School Playground

	Total Group						Playground Group[a] After 14 Months (N=19)			
	After 1 Month (N=159)		After 6 Months (N=100)		After 14 Months (N=100)					
Item	N	%	N	%	N	%	N	%	χ^2 (df=3)[b]	p
Identified event as a stressor	138	87.0	53	53.0	34	34.0	13	68.4	20.78	0.0001
Fear when thinking of event	108	68.0	57	57.0	48	48.0	15	78.9	12.54	0.006
Intrusive imagery	73	45.9	29	29.0	17	17.0	11	57.9	28.92	<0.0001
Intrusive thoughts	80	50.5	33	33.0	22	22.0	12	63.2	25.50	<0.0001
Bad dreams	73	46.0	31	31.0	20	20.0	8	42.1	8.82	0.03
Fear of recurrence	116	73.0	50	50.0	38	38.0	12	63.2	7.70	0.05
Loss of interest	108	68.0	12	12.0	6	6.0	3	15.8	6.03	0.11
Wish to avoid feelings	92	57.7	24	24.0	20	20.0	11	57.9	24.22	<0.0001
Detachment	34	21.4	9	9.0	5	5.0	2	10.5	2.55	0.47
Jumpy/nervous	102	64.0	35	35.0	22	22.0	10	52.6	16.20	0.001
Sleep disturbance	86	54.0	26	26.0	18	18.0	11	57.9	14.30	0.003
Guilt feelings	22	14.0	18	18.0	14	14.0	5	26.3	4.99	0.17
Interference with learning	45	28.3	11	11.0	7	7.0	4	21.1	7.17	0.07
Difficulty concentrating	45	28.3	17	17.0	10	10.0	4	21.1	4.28	0.23
Avoidance of reminders	108	68.0	70	70.0	66	66.0	17	89.5	11.05	0.01
Upset by thought of event	122	77.0	59	59.0	47	47.0	16	84.2	15.42	0.01
Feels alone	—	—	20	20.0	12	12.0	6	31.6	10.46	0.02

[a] Children who were on the playground during the attack.

[b] Difference between the chidren on the playground and the total group for each item at 14 months.

0.001; 4×4 χ^2=22.3, df=9, p=0.008), at 6 months (r_s=0.48, N=100, p<0.001; 4×4 χ^2=41.4, df=9, p<0.001), and at 14 months (r_s=0.51, N=100, p<0.001; 4×4 χ^2=42.1, df=9, p<0.001). At 14 months, 74% (N=14) of the 19 children who had been on the playground during the attack continued to report symptoms of PTSD; 81% or more of the 81 children who had not been directly exposed reported no PTSD symptoms. The presence of PTSD symptoms at 14 months could also be predicted by the severity of the child's original reaction as indicated by the index score (r_s=0.39, N=100, p<0.001; 4×4 χ^2=28.9, df=9, p<0.001). Children who did not have an acute reaction rarely reported a reaction 14 months later (1%, N=1).

The children were asked how well they knew the deceased victim and were rated as knowing her well, some, or not at all. Greater acquaintance with the victim was significantly related to higher reaction index scores, however, only for the less exposed children (Acquaintance by Exposure, F=2.18, df=6, 88, p<0.05). For children who had been on the playground, there was no significant difference between acquaintance levels. While acquaintance with the victim was associated with higher reaction index scores for the children who had been in the school, not at school, and off track, in contrast to the acute phase their scores were not in the clinically significant range.

Grief scores were analyzed with respect to acquaintance with the victim and degree of exposure to the event. Greater grief was associated with greater acquaintance with the deceased (F=31.1, df=2, 97, p<0.0001). The effect of exposure on grief reactions was not significant.

We examined the presence or absence of each individual symptom across the four exposure levels by using a 2×4 chi-square analysis (table 1). With the exception of detachment, which was rarely reported (5%), the greater the exposure to the attack, the greater the percentage of children reporting each symptom at 14 months. The percentage who reported each symptom was reduced over time, with two exceptions: more children reported guilt feelings and avoidance of reminders at 6 months than at 1 and 14 months.

During our initial screening, over half of all of the groups reported considering the event to be an extreme stressor, fear when thinking of it, fear of a repeat incident, jumpiness, and avoidance of reminders. At 14 months, more than 50% of all groups reported only avoidance of reminders. For the directly exposed children, there was some selective recovery, including fewer reports of bad dreams, detachment, reduced interest in activities, and interference with learning. A majority of them, however, continued to report considering the event to be an extreme stressor, fear when thinking of it, intrusive thoughts, intrusive sounds and images, fear of a repeat incident, a wish to avoid feelings, jumpiness, and sleep disturbance, and significantly more reported difficulty paying attention and feeling alone with their distress.

As in the acute-phase study, few children (14%) reported feelings of guilt. When they did, the children reported feeling guilty for being unable to provide aid, being safe when others were harmed, or taking actions that they believed endangered others. While guilt had no effect on the reaction index scores of the children who had been on the playground, it was associated with higher scores for each of the other groups. The mean reaction index score of the children not directly exposed who experienced guilt feelings equaled that of the directly exposed children (mean=8), in contrast to a mean score of 2 for the children not directly exposed who were without guilt feelings ($F=15.4$, df=1, 92, $p=0.001$).

Four symptoms not included in the original screening were measured. There were significantly more somatic complaints by the children who had been on the playground or in the school both at 6 months ($\chi^2=11.6$, df=3, $p<0.01$) and at 14 months ($\chi^2=13.02$, df=3, $p<0.005$) than by the nonexposed children. There was no significant difference among children at different exposure levels in omen formation, new fears, or change in eating behavior at 6 and 14 months.

In addition to the effects of a previous trauma and worry about a significant other, the effects of an intervening trauma were measured at the 14-month follow-up. As in the acute-phase study, previous trauma and worry about a significant other had no significant effect on reaction index scores. The number of children reporting worry about a sibling increased linearly the farther away the child had been from the violence ($\chi^2=12.25$, df=1, $p=0.0005$).

With only 14 children reporting an intervening trauma, definitive statements cannot be made about its effects. A greater percentage of children in each exposure group who reported an intervening trauma had new fears and somatic complaints 6 and 14 months after the event. There was, however, no significant difference or interaction between exposure groups for an intervening trauma ($F=2.38$, df=1, 92, $p=0.13$) and no difference when exposure was used as a covariate ($F=3.32$, df=1, 97, $p=0.07$).

DISCUSSION

This study demonstrated symptoms of chronic PTSD in highly exposed children up to 14 months after a sniper attack at their school. As demonstrated for adults (1, 2), proximity to the violence and degree of life threat remained the primary predictors of continued posttraumatic stress reactions. There was a rapid diminution of symptoms in those less exposed. Children in the school whose teachers put them under desks and in closets in preparation for a more direct assault were not significantly different after 14 months from the unexposed children.

After 14 months, the fear of recurrence and horror over the violence, which had initially affected the entire school community, had faded except in the most directly exposed children. While some of the children who had been on the playground had been in safer areas, most of them had been under direct threat and/or had witnessed injury or death. No reality-based reappraisal by the children in the line of fire could minimize the degree of threat to their lives, whereas the children who had been in classrooms no longer appraised the event as an extreme stressor, perhaps because they had reassessed the threat.

The etiological importance of intrusive imagery has been reported for adult PTSD (8, 9); this study underscored that finding for children. As in the acute-phase study, intrusive phenomena remained prominent for children who had been on the playground. They described continued thoughts and images of the deceased child, injured and bleeding classmates, bullets striking the nearby pavement, sounds of gunfire, and cries for help. Although reports of dreams with an apparent traumatic content diminished over time, clinically, it was found that the dreams recurred sporadically in response to traumatic reminders.

Like Cambodian children studied years after exposure to long-term wartime violence (10), over time these children often suffered their persistent intrusive thoughts and other posttraumatic symptoms silently. While detachment from others diminished significantly over time, the highly exposed children remained emotionally avoidant and alone with their distress. One indication of the children's continued distress was the significant level of their somatic complaints after 14 months.

Fourteen months is a substantial period of time in a school-age child's life. Symptoms of PTSD may affect a number of factors in the developmental process, including cognition, attention, initiative, social interaction, outlook, personality style, self-esteem, and impulse control (4, 11–13). In view of the potential impact of PTSD, the results of this study have implications for early intervention, triage, and design of mental health services for children exposed to disaster.

While it has been beneficial to respond, for example, to a total school population after a traumatic event, strategies of intervention need to address the differential experiences of the children involved (14). After community disaster or violence, it is essential to keep good records of children's exposure levels. Highly exposed children will require special attention.

The effect of witnessing injury and death on children's posttraumatic reactions and recovery suggests the need to minimize, when possible, their exposure to injured, mutilated, or dead bodies. The media can be a source of unnecessary secondary exposure through exhibiting blood, corpses, or mutilation. After the sniper attack, the deceased girl was carried into a classroom where there were other children, thereby inducing traumatic images in previously less traumatized children.

In addition to degree of exposure, other factors appear important to the triage of children after exposure to violence. In this study, knowing the deceased victim was associated with a greater number of posttraumatic stress symptoms in the less exposed children, perhaps by changing their perception of their involvement in the event. Grief reactions, however, occurred independent of exposure. Moreover, feelings of guilt were associated with a greater response in the less exposed children confirming the importance of guilt feelings as an associative feature of PTSD. These findings suggest that strategies of intervention with children exposed to violence also need to address bereavement and feelings of guilt.

Worry about a significant other had no effect on PTSD responses. Clinically, however, this experience resulted in continued concerns about the whereabouts and safety of significant others. For example, children reported chronic waking several times nightly to check on a sibling who had been endangered during the sniper attack. This increase in separation anxiety and the concomitant changes in interpersonal relationships indicate an additional reason for intervention.

While children who had experienced previous traumas did not have more symptoms specific to this sniper attack, they did have renewed symptoms related to the previous experiences, including the PTSD symptoms of intrusive imagery and thoughts, bad dreams, disturbed sleep, upset, jumpiness, and feelings of aloneness. Exposed children usually spoke first of the current event, while unexposed children focused primarily on the previous events. Although there were too few to analyze, the parents who reported their own previous exposure to violent traumas appeared to have a difficult time responding to their children's reactions.

Silver and Wortman (15) have discussed the added distress caused by unwarranted expectations of recovery after undesirable life events. While reporting a significant rate of symptoms after 14 months, many of the exposed children in our study expressed the expectation that they should have already recovered. Better professional education and public awareness about the nature and course of children's posttrauma reactions to violence can help to normalize understandable reactions and expectable course of recovery.

In 1985, the U.S. Surgeon General, C. Everett Koop, declared that exposure to actual violence is a major public health concern. Making children the object of wanton violence is a disturbing trend in our society. Interrupting this epidemic of violence is a priority. The findings of this study suggest that psychological first aid at schools exposed to violence must be accompanied by a more comprehensive program of follow-up for highly exposed children.

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Psychiatric Status of Adolescents Who Had Extreme Temperaments at Age 7

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Two temperamentally extreme (extremely easy and extremely difficult) subgroups of children were selected at the age of 7 years from a large random sample of the general population of Quebec City. The clinical status, family functioning, IQ, and academic performance of these children were reassessed at 12 and 16 years of age. Findings suggest that extreme temperament at age 7 predicts psychiatric status in preadolescence and adolescence only when family functioning is also taken into account. The adolescents who had been temperamentally difficult children and who were living in families with dysfunctional behavior control displayed more clinical disorders.

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The combination of longitudinal and cross-sectional epidemiologic designs constitutes a powerful means of scrutinizing the mechanisms involved in the development of psychopathology in children and adolescents (1). This combination may also help to evaluate the risk associated with extreme temperament (2). To be widely considered and used in the practice of child psychiatry, the concept of temperament has to be reliably measurable in clinical populations and in the general population. In addition, temperament, although somehow associated with psychopathology, must prove to be distinct from a clinical disorder or from other aspects of personality in terms of its phenomenology (3) and biological basis (4). Temperament must also be shown to be involved in the causative processes leading to serious or persistent psychopathology in childhood, thus contributing to cause-specific and efficient therapeutic interventions. Understandably, child temperament has not yet met all of these requirements (5).

Several models of temperament are currently under study (6). We recently argued that temperament should already matter to the practitioner of child psychiatry and child psychology (2). We based this argument on four pieces of empirical evidence. First, a temperamental cluster, closely similar to the New York Longitudinal Study easy–difficult cluster (7), has been replicated many times as a first factor (factor 1) from a principal component analysis in the general population (8, 9) and in clinical populations (10) of children aged 4–8 months to 7 years in Quebec and elsewhere (11). Such findings indicate that the composite which makes up factor 1 (withdrawal from new stimuli, low adaptability, high emotional intensity, and negative mood) significantly distinguishes children at different age levels, at least until age 8 (12). Second, extremely negative features in the easy–difficult cluster are associated with clinical behavior disorders in children 4–5 years of age and older (3, 13); however, contrary to the argument of some (14), extremely adverse temperament has not been found to be automatically equivalent to a clinical disorder across childhood in the general population (4) and in clinical populations (10). Third, recent evidence (10) suggests that extreme temperaments on different composites are associated with different types of psychopathology in children referred for psychiatric treatment. Fourth, we found that children who had extremely difficult temperaments on factor 1 at age 7 (who represented the extreme 10% of children selected from a large random sample of the general population of Quebec) displayed more clinical disorders at age 12 than did children who had extremely easy temperaments at age 7 (15). Our data suggest that between the ages of 7 and 12, dysfunctional behavior control in the family increased the risk of disorders in the children who were temperamentally difficult at age 7, whereas superior behavior control considerably decreased that risk in such children.

In the present paper we report on the next follow-up of the same group of temperamentally extreme 7-year-olds at 16 years of age (mean age=16 years and 1 month).

We asked two questions in the present study. 1) To

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what extent does extremely difficult temperament at age 7 increase the risk of developing a clinical disorder between the ages of 12 and 16? 2) Is there a relationship between extreme temperament in children and a dysfunctional family in terms of behavior control that could increase the children's liability to disorders between the ages of 7 and 16?

METHOD

Sample

In 1979, we assessed twice, at a 4-week interval, the temperament of a random sample of 980 7-year-olds of Quebec City, using a French translation of the Thomas, Chess, and Korn Parent Temperament Questionnaire (9), as detailed in our previous report (15). From this sample, two extreme subgroups, balanced for sex and socioeconomic status, were followed up: 24 children with extremely difficult temperaments at age 7 (scoring higher than the 70th percentile on four or five of the five categories loading strongly on temperament factor 1 [approach/withdrawal, adaptability, intensity, mood, and distractibility]) and 15 children with extremely easy temperaments (scoring lower than the 30th percentile on at least three of the five categories) (15). The subjects had to present their extreme traits at both assessments at age 7. The rate of response was 85% in the random sample and 93% in the sample of extreme subjects. The cutoffs used for the two groups at age 7 correspond to the extreme 9%–10% on both ends of the temperament composite continuum.

Thirty-eight (97%) of the 39 children originally assessed as 7-year-olds were reached at age 16, 32 boys and six girls, and they and their families agreed to participate. Four (10%) of these children were in Hollingshead class I, five (13%) were in class II, nine (24%) were in class III, 14 (37%) were in class IV, and six (16%) were in class V.

Instruments

The children's clinical status at age 16 was evaluated by means of two structured psychiatric interviews conducted in their homes by a psychiatrist (C.C.). The instruments used were the Diagnostic Interview Schedule for Children and the parents' version of the Diagnostic Interview Schedule for Children (16). These are standardized interviews that take 60 to 90 minutes each to administer and were used to make *DSM-III* diagnoses for the children for the preceding 12 months. Twice we administered a self-rating questionnaire, the Youth Self-Report and Profile, developed by Achenbach and Edelbrock (17) for boys and girls ages 11 to 18. This questionnaire consists of 112 items divided into eight dimensions plus two scales for global symptoms, one for internalized symptoms and one for externalized symptoms. The 3-week test-retest reliabilities (intraclass correlations) for this sample were 0.86 (externalized symptoms scale) and 0.84 (internalized symptoms scale). At the previous follow-up at age 12, the child's clinical status had been evaluated by means of two interviews conducted independently by two psychiatrists (15).

In order to verify its stability, we reassessed family functioning at the second follow-up, when the children were 16 years old. A semistructured interview based on the McMaster model of family functioning (category of behavior control) (18, 19) was conducted at the child's home with the whole family; the same procedure was followed during the first follow-up, when the children were 12 years old (15). The category of behavior control in the McMaster model taps the clarity of the family rules, the parental consensus about rules, and the consistency of the parental response when the rules are violated by the children. The interrater reliabilities of this interview were satisfactory at the first and second follow-ups ($r_s=0.79$ and $r_s=0.85$, respectively) (19). We observed a satisfactory degree of stability of family functioning in terms of behavior control from the age of 12 to the age of 16. A different investigator, blind to the family scores obtained when the children were 12 years old, interviewed the family 4 years later and rated the McMaster model behavior control scale. (A score of 4 or less indicated average functioning or dysfunction; a score greater than 4 indicated superior functioning.) The families who had been rated as having superior, average, or dysfunctional qualities when the children were 12 tended to remain in the same categories of functioning when the children were 16 (Cohen weighted kappa=0.45, Z=2.65, $p<0.01$ with the weights $w_{ij}=[i-j]^2$, N=37). To maintain the longitudinal perspective of the developmental effects that were studied, the behavior control scores assessed at the 12-year follow-up were used in the analyses.

The adolescents' perception of their self-image at age 16 was measured twice, at a 4-week interval, by using a French translation of the Offer Self-Image Questionnaire for Adolescents (20). Three dimensions were used: 1) the vocational-educational goals scale, assessing the adolescent's planning for a vocational future, 2) the mastery of the external world scale, quantifying the adolescent's adaptation to the immediate environment, and 3) the superior adjustment scale, evaluating the adolescent's view of how he or she coped with significant people and the world. The test-retest reliabilities (intraclass correlations) of our French translation were satisfactory: 0.82, 0.66, 0.78, and 0.88 for the vocational-educational goals scale, the mastery of the external world scale, the superior adjustment scale, and the global score, respectively.

Procedure

The study was set up in such a way that all the investigators who had contact with or made clinical judgments about the subjects at age 16 were blind to all previous family, clinical, and temperament data.

The data were gathered through four home visits by different investigators in order to keep the assessments independent. In a first visit, explanations were given and a signed consent was obtained from the adolescents and their parents. In a second visit, the two structured interviews were performed and audiotaped, one with the adolescent alone and one with the parents alone. The adolescent was given the temperament questionnaire, the Youth Self-Report and Profile, and the Offer Self-Image Questionnaire for Adolescents. The order in which the questionnaires were to be filled out was predetermined. The adolescents were instructed to fill out no more than one questionnaire a day and to mail them no more than 2 weeks later. Three weeks after they had done so, they were asked to complete a second set of the same questionnaires. On a third home visit, an experienced psychologist (P.B.) administered the WISC-R. On the fourth visit, another investigator (H.B.), a senior therapist experienced with the McMaster model, assessed the family functioning. The high school academic charts were requested from the adolescents' school principals.

To establish the clinical status of the adolescents, another psychiatrist (J.T.), also blind to the temperament scores and all other data, rated the audiotapes of the structured interviews. Each investigator independently made a clinical judgment on the presence or absence of a diagnosis on axis I of *DSM-III.* They also based their clinical judgments on the "clinical-diagnostic" definition of a psychiatric disorder described by Rutter (21). They also rated the severity of the disorder using the Clinical Global Impression scale (CGI) (22). The agreement between psychiatrists was 84% on the presence or absence of diagnosis and 84% on the type of *DSM-III* diagnosis. Concerning the diagnoses for which agreement was not obtained at first (N=6), a consensus on a final diagnosis was arrived at with all clinical information available at age 16 except for temperament and family functioning rating. The 14 adolescents who were given a clinical diagnosis at age 16 had more symptoms on the externalized symptoms scale (Wilcoxon rank test, Z=3.28, p=0.001) and the internalized symptoms scale (Wilcoxon rank test, Z=2.79, p<0.01) of the Youth Self-Report and Profile than did the 24 adolescents who were not given diagnoses.

RESULTS

Extreme Temperament at Age 7 and Clinical Status at Age 16

The relationship between extreme temperament at age 7 and the presence of definite psychiatric diagnoses at age 16 was examined first. A definite diagnosis was given to four (27%) of the 15 temperamentally easy subjects and 10 (43%) of the 23 temperamentally difficult children ($\chi^2=0.50$, df=1, p=0.45, Yates's correction). Thus, clinical status at age 16 was not significantly associated with extreme temperament at age 7. However, the children who were temperamentally difficult at age 7 had significantly more symptoms at age 16 on the externalized symptoms scale (Wilcoxon rank test, Z=2.06, p<0.05) and the internalized symptoms scale (Z=2.61, p<0.01) of the Youth Self-Report and Profile.

TABLE 1. Presence or Absence of Clinical Diagnoses and Family Behavior Control Functioning of 38 Adolescents Who Had Extremely Difficult or Extremely Easy Temperaments at Age 7[a]

Family Functioning at Age 12 and Presence or Absence of Clinical Diagnoses at Age 12, Age 16, or Both	Extreme Temperament at Age 7	
	Easy (N=15)	Difficult (N=23)
Superior behavior control (N=17)[b]		
Adolescents with clinical diagnoses	2	2
Adolescents without clinical diagnoses	6	7
Average or dysfunctional behavior control (N=21)[b]		
Adolescents with clinical diagnoses	3	14
Adolescents without clinical diagnoses	4	0

[a] The results of stepwise logistic regression (BMDP) applied to the data are 1) step 1, behavior control ($\chi^2=13.26$, df=1, p<0.001); 2) step 2, temperament at age 7 ($\chi^2=4.43$, df=1, p<0.04); 3) step 3, interaction of temperament and behavior control ($\chi^2=6.47$, df=1, p=0.01).

[b] McMaster model of family functioning behavior control scale.

Extreme Temperament at Age 7 and Clinical Status at Ages 12 and 16

We looked at the presence of clinical disorders at either 12 or 16 years of age or at both ages in the two extreme temperamental groups selected at age 7, taking into account their family situation in terms of behavior control, for two reasons. First, we had found an association between extreme temperament at age 7 and clinical status at age 12 in the children in this sample whose families had behavior control scores indicating dysfunction (15). Second, in the current analysis we observed an association between temperament at age 7 and the number of symptoms at age 16.

A stepwise logistic regression analysis (BMPD) was applied to the data in table 1; clinical status was the response variable. The improvement in chi-square and the values at each step are provided in table 1. The logit main effects (behavior control and temperament) model was tested against the model including their interaction. The improvement in chi-square value when the interaction was entered ($\chi^2=6.47$, df=1, p=0.01) suggests the presence of a second-order interactive effect of temperament and behavior control on clinical status; 82% of the subjects were correctly classified by this analysis. In other words, the effect of temperament on clinical outcome depended on the level of behavior control in the family and vice versa. Indeed, the data given in table 1 suggest that the effect of extreme tem-

TABLE 2. Characteristics at Ages 7, 12, and 16 of 38 Adolescents With Extremely Easy or Extremely Difficult Temperaments at Age 7

Subject	Sex	Extreme Temperament at Age 7	SES[a] at Age 7	Family Functioning Score at Age 12[b]	IQ at Age 16	*DSM-III* Diagnoses at Age 12		*DSM-III* Diagnoses at Age 16	
						Diagnosis	Severity[c]	Diagnosis	Severity[c]
7	M	Difficult	2	2	84	Oppositional disorder Attention deficit disorder	5 5	Oppositional disorder Attention deficit disorder with hyperactivity Atypical stereotyped movement disorder	5 5 3
10	M	Difficult	4	3	102	Avoidant disorder	3	Hyperanxiety	6
25	F	Difficult	4	4	97	Oppositional disorder Attention deficit disorder	5 3	Oppositional disorder	3
38	M	Difficult	5	2	114	Oppositional disorder Attention deficit disorder	4 2	Oppositional disorder Attention deficit disorder with hyperactivity	5 3
16	M	Difficult	4	5	123	Oppositional disorder	5	Oppositional disorder	4
15	M	Difficult	5	2	82	Oppositional disorder	4	Oppositional disorder Residual attention deficit	4 4
23	M	Difficult	4	2	120	Oppositional disorder	3	Oppositional disorder	5
30	M	Difficult	1	5	112	None	—	Oppositional disorder	4
18	M	Difficult	4	3	116	None	—	Conduct disorder, social, nonaggressive Oppositional disorder	3 3
1	F	Difficult	5	3	96	None	—	Conduct disorder, social, nonaggressive Oppositional disorder Dysthymic disorder	4 5 3
12	M	Easy	3	3	116	None	—	Oppositional disorder	4
13	M	Easy	4	3	87	None	—	Dysthymic disorder	4
21	M	Easy	3	3	102	None	—	Oppositional disorder Dysthymic disorder	4 2
34	M	Easy	4	5	92	None	—	Conduct disorder, social, nonaggressive Cannabis dependency Multiple dependencies	3 4 4
5	M	Difficult	3	3	106	Oppositional disorder	3	None	—
17	M	Difficult	5	2	121	Oppositional disorder	5	None	—
35	M	Difficult	2	4	115	Oppositional disorder	3	None	—
39	M	Difficult	4	3	93	Oppositional disorder	4	None	—
33	M	Difficult	4	4	107	Oppositional disorder	2	None	—
6	M	Difficult	3	4	92	Oppositional disorder	3	None	—
4	M	Easy	5	5	89	Oppositional disorder	2	None	—
3	M	Difficult	3	5	111	None	—	None	—
26	M	Difficult	4	5	92	None	—	None	—
14	M	Difficult	2	5	100	None	—	None	—
32	F	Difficult	1	6	100	None	—	None	—
8	M	Difficult	3	6	123	None	—	None	—
19	M	Difficult	4	6	91	None	—	None	—
37	M	Difficult	3	5	128	None	—	None	—
22	F	Easy	3	5	116	None	—	None	—
27	M	Easy	2	4	104	None	—	None	—
31	M	Easy	4	4	123	None	—	None	—
40	M	Easy	4	5	105	None	—	None	—
29	F	Easy	1	5	121	None	—	None	—
20	F	Easy	5	4	95	None	—	None	—
36	M	Easy	2	5	99	None	—	None	—
2	M	Easy	4	4	92	None	—	None	—
11	M	Easy	3	7	122	None	—	None	—
28	M	Easy	1	5	111	None	—	None	—

[a] Socioeconomic status according to the Hollingshead two-factor index of social position.

[b] McMaster model of family functioning behavior control scale; a score of less than 4 indicates dysfunction; 4 indicates normal functioning; more than 4 indicates superior functioning.

[c] CGI scale rating.

perament at age 7 on clinical outcome prevails in families with dysfunctional behavior control. All 14 of the children with extremely difficult temperaments at age 7 who were living in families with average or dysfunctional behavior control were given a clinical diagnosis at age 12, at age 16, or at both ages, but only two of the nine children with extremely difficult temperaments at age 7 who were living in a family with superior functioning were given a diagnosis.

The qualitative analysis of the longitudinal data given in table 2 allows three other observations. First, two groups of children appear strikingly different: the seven children who were given clinical diagnoses at both 12 and 16 years of age and the 17 children who were never given clinical diagnoses. All seven children with clinical diagnoses at ages 12 and 16 were temperamentally difficult at age 7, and six were living in dysfunctional families in terms of behavior control. Conversely, seven of the children with extremely difficult temperaments at age 7 were not given a clinical diagnosis at either age 12 or age 16, and all of these children were living in families with superior behavior control (six of seven versus none of seven; $\chi^2=7.29$, df=1, $p<0.01$, Yates's correction). This provides, in another way, some evidence of a longitudinal interaction between family behavior control and extremely difficult temperament.

Second, table 2 shows that the clinical diagnoses given to the temperamentally difficult children at age 16 were predominantly externalized (oppositional disorder and attention deficit disorder), as they were at age 12.

Third, the two extreme temperamental groups selected at age 7 displayed no difference in terms of intellectual development at 16 years of age, as assessed by the WISC-R (the mean±SD IQ of the 23 adolescents who had been temperamentally difficult children was 105±13.3; for the 15 adolescents who had been temperamentally easy it was 105±12.6). Moreover, in terms of academic performance in high school, we found no observable difference between the two extreme temperament groups. The academic charts over the preceding 2 years were categorized according to the type of class attended (regular or vocational), the number of subjects failed, and the percentage of school terms during which they were placed above or below the mean of the group for mathematics and French.

Finally, the children who had been extremely difficult 7-year-olds had lower self-images as adolescents (as measured by the Offer Self-Image Questionnaire for Adolescents) than did those who had been extremely easy 7-year-olds ($Z=2.5$, $p=0.01$, for the superior adjustment scale; $Z=2.0$, $p=0.05$, for the mastery of external world scale; $Z=1.7$, $p=0.09$, for the vocational-educational goals scale; and $Z=-2.15$, $p=0.03$, for the global score, Wilcoxon rank test).

DISCUSSION

This 9-year follow-up suggests that extremely difficult temperament at age 7 (withdrawal from novelty, low adaptability, high intensity, and negative mood) is associated with the presence of clinical disorders in preadolescence and adolescence. However, the present data suggest that child temperament by itself, even if extreme, is not as good a predictor as it is when the effect of family behavior control is taken into account. This appears even clearer at this second follow-up than it was in the previous follow-up of this group of children (15). All of the children in our sample who had extremely difficult temperaments at age 7 and who lived in dysfunctional families were given a clinical diagnosis in preadolescence or adolescence. For children in families with superior behavior control functioning, however, no difference in outcome was apparent between the extremely difficult and the extremely easy children. This interaction between temperament and family functioning is also obvious when the temperamentally difficult children who were given clinical diagnoses at both age 12 and age 16 are compared with those who were not given clinical diagnoses at these ages; the former lived in dysfunctional families, whereas the latter lived in functional families. Of course, our research design only points to the triangular association of extremely difficult temperament, dysfunctional behavior control, and the appearance of disorders. It cannot discern, for instance, the direction of the process: does extreme temperament favor a progressive decompensation of family behavior control or does poor behavior control lead to extreme temperament?

Our children with extreme temperaments represented the extreme 10% of the distribution in the general population. Very few other studies on the predictive value of early temperament up to adolescence exist in the literature. In the New York Longitudinal Study, Thomas and Chess (23) reported a slight association between temperament in preschool years and adjustment in late adolescence and young adulthood (18–22 years of age). The difference in the size of the association they found and that which we found may depend on many factors. First, their measurement of temperament was taken only in preschool years (no assessment was made in middle childhood), and the period of their follow-up was longer. Second, they did not study the extremes from a random sample of the general population.

The diagnoses made on the basis of interviews with the children at age 16, like those made when they were 12 years old (15), were especially of an oppositional and externalized nature at home. However, it is noteworthy that the adolescents who were temperamentally difficult at age 7 described themselves at age 16 on the Youth Self-Report and Profile as much on the internalized pole ($r_s=0.43$, df=37, $p<0.01$) as on the externalized one ($r_s=0.34$, df=37, $p<0.05$). They also defined their self-image as poorer on the Offer Self-Image Questionnaire for Adolescents. Additionally, we have previously reported that children with extremely difficult temperaments on factor 1 had scores on the Conners teacher scale indicating more internalization at age 7 (2) and that they had scores on the Rutter teacher scale indicating more internalization at age 12 (15). These children would thus have externalized symptoms at home but internalized symptoms outside the home environment. All this corroborates a developmental hypothesis that we recently formulated (13): when their families are dysfunctional in behavior control, temperamentally difficult young children (who withdraw from new situations, adapt poorly, are very intense, and have an overall negative mood) are more likely to develop clinical symptoms of opposition and externalization in the family environment, in which they are at ease and to which they are more adapted. However, outside the family, in novel or social situations that call on their adaptive abilities (such as school), these children are more likely to display internalized clinical symptoms. Similarly, later, as adolescents, they would also tend toward internalization because of the increasing number of social situations calling for greater personal abilities to approach and adapt to novel situations.

The present longitudinal findings indicate that, up to adolescence, extremely difficult temperament in young children leads to a clinical picture of a mixture of externalized and internalized symptoms and that each group of symptoms is specific to the type of environment. However, the two original extreme temperament groups had identical academic outcomes in high school and the same intellectual abilities (IQ) at age 16. This is compatible with our previous findings in this study group when they were in primary school (24), when there was only a very slight association with academic performance. Thus, extremely difficult temperament on factor 1 appears longitudinally associated with clinical but not with academic outcome. This result is congruent with the already well-established finding that the correlates of behavior disorders in childhood are not the same as those of cognitive or academic outcome (25, 26). Of course, our data do not preclude the possibility that temperament traits other than those used to define difficult temperament in this study are more related to academic outcome (27).

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The Natural History of Alcohol Abuse: Implications for Definitions of Alcohol Use Disorders

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Is the DSM-III-R *category of alcohol abuse validly differentiated from the* DSM-III-R *category of alcohol dependence, or is abuse primarily a mild, prodromal condition that typically deteriorates into dependence? A 4-year longitudinal epidemiologic study of male drinkers provided data to answer this question. The study used identical questions at baseline and follow-up. At follow-up, 70% of the subjects who were initially classified as alcohol abusers were still abusers or were classified as remitted. This contrasted significantly with outcome in the subjects who initially reported alcohol dependence. Although additional research is needed, these results indicate that alcohol abuse often has a course distinct from that of alcohol dependence.*

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The definitions of alcohol use disorders have changed considerably through the successive sets of diagnostic criteria developed for psychiatric research and clinical diagnosis. In the earlier Feighner criteria (1) and Research Diagnostic Criteria (2), only one alcohol use disorder, "alcoholism," was defined. In *DSM-III,* alcohol use disorders were divided into two categories, alcohol abuse and alcohol dependence. It is now clear that the abuse category contained many symptoms ordinarily considered to indicate dependence. Numerous factors, including research challenging the validity of the *DSM-III* distinction between abuse and dependence (3), led to considerable revision of the alcohol use disorders in *DSM-III-R.*

The *DSM-III-R* definition of alcohol dependence was heavily influenced (4) by the concept of alcohol dependence initially proposed by Edwards and Gross (5). In *DSM-III-R,* the diagnostic criteria were modified to emphasize not only physiological dependence but also subjective indicators of impaired control, increased salience of drinking, and indirect indicators of impaired control such as continued drinking despite health or social problems. Abuse became a residual category for those who never met dependence criteria but who drink despite social, occupational, psychological, or physical problems related to alcohol or in hazardous situations such as driving. Before the publication of *DSM-III-R,* alcohol abuse as a category had been dropped entirely on the grounds that determining the diagnosis of a substance use disorder on the basis of its social consequences placed insufficient emphasis on the "essential process" of the disorder (5). The abuse category was reintroduced in response to the concerns of some clinicians who felt the need for a diagnosis when substance use led to impairment without dependence indicators. The statements in *DSM-III-R* that abuse applies to those "who have not *yet* developed . . . dependence" (italics added) (6) and to those "who have only recently started" taking the psychoactive substances (i.e., those who started drinking only recently) appear to indicate an assumption that abuse constitutes a mild condition prodromal to dependence.

If the most likely outcome of alcohol abuse is a diagnosis of alcohol dependence, then the validity of the distinction between abuse and dependence is somewhat challenged because the abuse category serves only to identify early, mild manifestations of the disorder of dependence. In this case, perhaps abuse should be dropped and the severity threshold for dependence lowered to include those who would now be diagnosed as nondependent abusers. However, if the assumption about the likely evolution of alcohol abuse into dependence is false, then dropping the abuse category and broadening dependence would add heterogeneity to dependence, which is already quite a heterogeneous category.

For the purposes of revising the criteria for alcohol use disorders in *DSM-IV,* as well as for better understanding the nature of the alcohol use disorders, information on the longitudinal relationship of abuse to dependence becomes especially important. In particular, follow-up studies of alcohol abusers in the general

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population offer the possibility of learning whether alcohol abuse remains a consistent condition or typically evolves into alcohol dependence. Concurrent follow-up of alcohol-dependent individuals provides the opportunity to determine whether the most likely outcome of abuse contrasts with the outcome of dependence.

Although follow-up studies of drinking (7–9) and drinking problems (10, 11) have been reported, they either focused entirely on consumption patterns (7–9) or used measures designed for other purposes (10, 11) and did not attempt to clearly differentiate aspects of alcohol abuse from alcohol dependence.

At this writing, *DSM-III-R* has been published for only 2 years. Clearly, not enough time has elapsed since its publication for the completion of studies designed specifically to examine the natural history of alcohol abuse as defined in *DSM-III-R*. However, a fresh look at some older data provides an unexpected source of information on this current research question. These data come from a 1973 follow-up study of men initially interviewed in a 1969 national survey of drinking practices and problems. The drinking practices and problems of the subjects were evaluated extensively in the 1969 survey and at the 1973 follow-up. Obviously, the *DSM-III-R* concepts of alcohol abuse and dependence were not evaluated specifically in this study. However, the richness of detail in the data allowed for the construction of variables analogous to the *DSM-III-R* categories of alcohol abuse and dependence for both the initial and the follow-up evaluations. Construction of these variables allowed us to test the hypothesis that the outcomes of subjects with initial indicators of alcohol abuse would differ from those of subjects with initial indicators of alcohol dependence.

METHOD

The original study from which these subjects were drawn was the third in an ongoing series of national surveys of drinking practices and problems conducted by the Alcohol Research Group, a National Institute on Alcohol Abuse and Alcoholism research center affiliated with the University of California, Berkeley. The original 1969 sample consisted of 978 men aged 21 to 59 years and is described in considerable detail by Cahalan and Room (12). The sample was drawn according to standard principles of national probability sampling; all households within 100 primary sampling units were prelisted and every *n*th one was selected by office staff (not interviewers). Eligible men within households were enumerated and selected by a random number device. The men were personally interviewed by trained survey interviewers. The interview was fully structured and incorporated the knowledge and experience of this research group in conducting the earlier national surveys on drinking practices and problems.

In this survey, primary sample units from urban areas were somewhat oversampled with the intention of obtaining a higher proportion of heavy drinkers in the sample. Weights were developed from the design of the sampling scheme to produce nationally representative rates. However, it was found that on virtually all variables aside from urbanicity, these weights produced only trivial differences in group comparisons (12). In 1969, 803 of the men were current drinkers.

In 1973, a follow-up study of these men was conducted. They were asked about their experiences with alcohol consumption and alcohol problems by using many of the same questions as those in the initial interview. The 3 years preceding the second evaluation constituted the time frame for the questions. Five hundred ninety-three men who had been current drinkers in the initial evaluation were followed up in 1973, a follow-up rate of 74%.

The questions used in constructing the present alcohol abuse and dependence variables were identical in the initial survey and at follow-up and used the same time frame (the preceding 3 years). The abuse and dependence indicators constructed from these items cannot be considered fully complete or perfect representations of abuse and dependence because not all aspects of the two disorders were covered, particularly for alcohol dependence. However, given the very limited amount of empirical research on the chronological relationships of abuse and dependence, we felt that the criteria were represented well enough to offer a useful empirical addition to theoretical work focused on this issue.

The areas covered in the indicators of *DSM-III-R* alcohol abuse included social, occupational, and physical problems as well as hazardous use (see table 1). The recent presence of these in men who were current drinkers (i.e., those who continued to drink despite these problems) was taken as a positive indicator of alcohol abuse.

Many but not all of the *DSM-III-R* criteria for alcohol dependence (criteria 1, 2, 3, 7, and 9) were represented in the data set (see table 1). Although the tolerance indicator is somewhat different from asking whether individuals needed to drink 50% more to get an effect (not included in the data set), the frequent consumption of a large amount of alcohol without accompanying intoxication seemed a reasonable proxy for the clinical concept of tolerance.

We did not include hazardous use or continued drinking despite problems among our dependence indicators because we wanted to keep the abuse and dependence categories separate. Note that the *DSM-III-R* criteria do not provide for entirely strict separation of abuse and dependence. Most aspects of the abuse criteria are embedded in the dependence criteria (criterion 4, hazardous use, and criterion 6, continued use despite problems). Therefore, a person meeting criteria for dependence might or might not also meet criteria for abuse. Also, an individual meeting only one of the criteria for abuse and only one for dependence would receive a diagnosis of abuse, not dependence, since three symptoms are required for dependence. For

TABLE 1. Alcohol Problems Used to Construct Indicators of Alcohol Abuse and Alcohol Dependence

Criterion	Representation From Items Included in the Data Sets
Alcohol abuse	
Recurrent social problems	Any of the following: 1. Threats by spouse to leave because of respondent's drinking 2. Respondent feels that his drinking has harmed his friendships, social life, home life, or marriage 3. Two or more of the following: a. Spouse objects to respondent's drinking b. Relatives object to respondent's drinking c. Friends object to respondent's drinking d. Neighbors object to respondent's drinking
Occupational problems	Two or more of the following: 1. Losing or nearly losing a job due to drinking 2. Quitting a job due to drinking 3. Being "high" or "tight" while on the job 4. Staying out of work due to hangovers 5. People at work object to respondent's drinking 6. Respondent feels drinking has harmed his work 7. Respondent feels drinking has harmed his employment or advancement opportunities
Health problems	One of the following: 1. A doctor suggested respondent cut down on drinking 2. Respondent feels drinking harmed his health
Hazardous use	Any of the following: 1. Injury to respondent due to his drinking 2. Injury to someone else due to respondent's drinking 3. Property damage due to respondent's drinking 4. Drinking and driving that resulted in legal problems
Alcohol dependence	
Often drinks more or longer than intended	One of the following: 1. Respondent found it difficult to stop drinking before completely intoxicated 2. Respondent kept on drinking after promising himself he would not
Desire or unsuccessful efforts to decrease drinking	Respondent tried to cut down or quit but did not manage to do so
A great deal of time spent drinking	Usually frequency of drinking three or more times a day
Marked tolerance	Respondent drank eight or more drinks at least once a week AND felt intoxicated once a month or less
Characteristic withdrawal symptoms	Respondent's hands shook a lot in the morning after drinking
Drinking for relief or avoidance of withdrawal symptoms	Respondent often drank first thing in the morning

the purposes of the present study, the level of overlap in the abuse and dependence categories seemed likely to obscure what might be learned about the predictive power of the categories when separated more cleanly. Therefore, three categories for subgrouping subjects were created to correspond to abuse and dependence but with the level of overlap reduced. The three categories were 1) neither abuse nor dependence indicators, 2) abuse indicators with no dependence indicators, and 3) dependence indicators with or without abuse indicators.

Of the 593 men who were current drinkers in the initial study, 71 (12%) were classified as abusers by the measure we constructed and 109 (18%) reported indicators of alcohol dependence. These 180 men were the subjects considered in this report. The demographic characteristics of all 593 men are given in table 2. Because weights were not developed specifically for the follow-up survey and weights for the original sample did not meaningfully influence most results aside from urbanicity (12), unweighted frequencies and proportions are presented. We used the standard chi-square test with Yates's correction to test whether follow-up outcome differed between men who initially reported indicators of abuse and men who initially reported dependence indicators.

RESULTS

Of the 71 men with initial indicators of alcohol abuse only, 50 (70%) reported indicators of alcohol abuse only (N=17) or remission (N=33) 4 years later, and the remainder, 30% (N=21), reported indicators of alcohol dependence with or without indicators of alcohol abuse. In contrast, of the 109 men with initial indicators of alcohol dependence, 50 (46%) still reported indicators of dependence 4 years later, and 59 (54%) reported indicators of abuse only (N=16) or remission (N=43). The differences in outcome between men with initial indicators of alcohol abuse only versus those with alcohol dependence were statistically significant ($\chi^2=4.12$, df=1, $p<0.05$).

TABLE 2. Demographic Characteristics and Presence of Alcohol Abuse or Dependence Indicators of 593 Male Drinkers at Initial Evaluation

Demographic Characteristic	No Abuse or Dependence Indicators (N=413)		Abuse Indicators Without Dependence Indicators (N=71)		Dependence Indicators With or Without Abuse Indicators (N=109)		Total Sample (N=593)	
	N	%	N	%	N	%	N	%
Age (years)								
20–29	94	22.8	25	35.2	36	33.0	155	26.1
30–39	112	27.1	23	32.4	25	22.9	159	26.8
40–49	118	28.6	13	18.3	27	24.8	159	26.8
50–59	89	21.5	10	14.1	21	19.3	120	20.2
Marital status								
Married	370	89.6	56	78.9	87	79.8	513	86.5
Separated	2	0.5	4	5.6	5	4.6	11	1.9
Divorced	7	1.7	2	2.8	3	2.8	10	1.7
Widowed	1	0.2	0	0.0	0	0.0	3	0.5
Never married	33	8.0	9	12.7	14	12.8	56	9.4
Race								
White	393	95.2	61	85.9	93	85.3	547	92.2
Nonwhite	20	4.8	10	14.1	16	14.7	46	7.8
Education								
Graduate level	54	13.1	7	9.9	6	5.5	67	11.3
College degree	44	10.7	3	4.2	9	8.3	56	9.4
Some college	97	23.5	18	25.4	14	12.8	129	21.8
High school degree	137	33.2	25	35.2	37	33.9	199	33.6
Some high school	38	9.2	10	14.1	12	11.0	60	10.1
Grades 7–9	31	7.5	7	9.9	24	22.0	62	10.5
Less than grade 7	12	2.9	1	1.4	7	6.4	20	3.4

DISCUSSION

The results reported here indicate that most of the men who initially reported alcohol abuse either remained in the abuse category 4 years later or had remitted from alcohol problems entirely. Alcohol abuse appears to pose a risk for later alcohol dependence, since about 30% of the initial abusers had evidence of alcohol dependence after 4 years. However, alcohol dependence was certainly not the inevitable fate of this group after a substantial period of follow-up. In contrast, about half of those with alcohol dependence indicators at initial interview reported alcohol dependence indicators at follow-up.

Several caveats about this study must be made. First, the *DSM-III-R* criteria for alcohol abuse and alcohol dependence were not represented fully, especially the criteria for alcohol dependence. Second, the sample included only men, leaving open entirely the question of the course of alcohol abuse in women. Third, a longer follow-up (or repeated follow-ups over a longer period of time) would have provided additional information about the eventual outcome of alcohol abuse and dependence. Fourth, these data were collected several years ago. Although assumptions are usually made about the universality of diagnostic criteria over time, we do not know if the same results would have been found if the study and the follow-up had been conducted more recently. Fifth, the sample sizes did not allow analyses of predictors of change or stability in status.

In addition, some investigators may have concerns that the follow-up results were influenced by the fact that the interviews were fully structured and conducted by nonclinicians, possibly giving rise to greater denial on the part of subjects with alcohol problems. There are a number of reasons why we think that this did not have a major influence on the reporting of changed status at follow-up. First, research is inconclusive on whether clinician interviewers obtain higher rates of alcohol problems than nonclinician interviewers in general population samples (13, 14). Second, the same type of interviewer was used for the initial and follow-up interviews, and thus, the background of interviewers could not have differentially affected the rates only in the follow-up study. Third, although clinical skills can obviously be extremely helpful in reducing denial, the use of clinician interviewers can bring different rating problems, such as the influence of preconceptions on clinical ratings, even in the face of clear stories to the contrary from the subject or patient. Thus, the use of survey interviewers represents a trade-off, but certainly this method has its own strengths.

A measurement strength of this study is that all relevant questions were asked of all current drinkers. Instructions to skip questions according to diagnostic hierarchies were not used, resulting in complete information on all variables among all current drinkers. Rather than using what Wing (15) has called a "top–

down" approach, in which only questions concerning specific diagnostic criteria are covered, the interview was constructed with a "bottom–up" approach. In this later approach, specified areas of psychopathology are covered because of their expected relevance to many research purposes. Good coverage of the relevant domains allows later combination of items for many purposes, including specific algorithms designed to represent currently defined diagnostic criteria. Through this approach, the data were (arguably) complete enough to be used for our purposes many years later, even after ideas about specific definitions of alcohol use disorders had changed several times. Although an interview designed according to such principles today would clearly include many more questions directly assessing current concepts of alcohol dependence, the process of covering numerous domains completely with all subjects allows for later analyses with items either combined into categories, scaled into continuous measures, or examined individually. Such complete coverage of alcohol problems is probably not possible in an interview that must also cover numerous additional axis I adult psychiatric disorders. However, when the research focuses specifically on alcohol, the "bottom–up" approach may yield a great deal of additional information that can be used for a number of purposes.

Despite the problems in the present study, the results represent the only longitudinal general population data known to us on the course of alcohol abuse and its relationship to alcohol dependence. To us, the results argue that a decision to drop alcohol abuse from *DSM-IV* and lower the threshold of alcohol dependence to include alcohol abusers would be premature at this point. According to these data, making such a change in the diagnostic criteria would increase the heterogeneity of a category that is already quite heterogeneous, decreasing both clinical and research utility. At the same time, additional longitudinal research on the natural history of alcohol abuse and dependence is urgently needed. This research should be conducted in samples of both men and women and should proceed with instruments designed to assess dependence indicators fully and accurately. Sample sizes should be large enough to evaluate the predictive power of subject and environmental characteristics on stability or change in status. Such research would lead to more valid definitions of alcohol use disorders and a better general understanding of these disorders.

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Cocaine/"Crack" Dependence Among Psychiatric Inpatients

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The authors studied 40 cocaine-dependent subjects admitted to psychiatric inpatient wards of a metropolitan hospital because of general psychiatric symptoms. The results indicate that the predominant form of cocaine administration (88%) was freebasing "crack." DSM-III-R *cluster B personality disorders (N=17) and schizophrenia (N=13) constituted the diagnoses for 75% of the sample. Compared to the schizophrenic patients in this cohort, the patients with cluster B personality disorders used cocaine in greater quantities and more frequently and began abuse of the drug at an earlier age. The escalation in urban areas of psychiatric hospitalizations attributed to use of crack may be largely related to psychiatric symptoms in cocaine-dependent patients with personality disorders as well as cocaine-induced psychopathology in schizophrenic patients.*

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The recent escalation of the use of the highly addictive form of cocaine called "crack" has risen to epidemic proportions. Cocaine and crack dependence among psychiatric patients is now generally recognized as a clinical problem of major importance (1, 2). When cocaine hydrochloride is converted into its freebase form (usually by adding sodium bicarbonate or another base), it vaporizes when heated and can easily be inhaled into the lungs. Crack is a convenient, crystalline, prepackaged amount of freebase cocaine that is usually sold in $5 or $10 vials. It is heated in a crack pipe, often making a crackling sound, and then inhaled. Cocaine in the form of crack has become accessible to a far broader range of the population, including those with chronic mental illnesses such as schizophrenia and those with disadvantaged psychosocial environments, i.e., the homeless and the indigent.

Patients with significant patterns of cocaine and/or crack dependence may come to metropolitan psychiatric emergency rooms with a variety of symptoms, as described in previous reports (3). Cocaine- or crack-dependent patients who are admitted to psychiatric inpatient units usually have coexisting psychopathology that can be coded on either axis I or axis II of *DSM-III-R* or both. The presenting symptoms may vary according to the pattern, quantity, and frequency of crack abuse as well as the environmental stressors and coexisting psychopathology. Accurate psychiatric diagnosis and optimal treatment of these patients will depend on an understanding of the interplay between observable symptoms, cocaine abuse patterns, and underlying primary psychiatric disorders.

The purpose of this study was to characterize and describe a sample of general psychiatric inpatients in a large metropolitan hospital who were dependent on cocaine or crack. The diagnostic spectrum and clinical profile of cocaine-dependent inpatients in a voluntary psychiatric drug treatment unit have been described in a previous report (4). However, to our knowledge, no prior study has examined the nature of cocaine or crack dependence in inpatients on general psychiatric wards.

METHOD

The subjects were 40 psychiatric inpatients at a large metropolitan general hospital, both involuntarily and voluntarily admitted, who met the *DSM-III-R* criteria for cocaine dependence on axis I. Thirty-seven of the 40 subjects also fulfilled the criteria for other axis I or axis II diagnoses. All were admitted to the general psychiatric inpatient service from the hospital's psychiatric emergency room after an evaluation by the psychiatric emergency room staff. Inpatients on the general psychiatric wards who were found by the ward psychiatrists to have any history of cocaine abuse were assessed. All subjects met the minimum criteria of at least weekly cocaine use, with a total consumption of cocaine worth at least $1,400 in the 3 months before admission. Those with abuse of any other substance, with the exception of alcohol and marijuana, during the month prior to admission were excluded. Depen-

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dence (*DSM-III-R* criteria) on any other substance during the past 3 months, except for prescribed methadone maintenance, was a criterion for exclusion. Approximately two-thirds of the sample assessed were excluded because of abuse of or dependence on other substances as just defined.

We used a 12-item questionnaire to assess the demographic profile of the sample. Psychiatric diagnoses were determined by means of the *DSM-III-R* criteria. A 72-item general substance abuse inventory was used to determine the broad extent and nature of drug and alcohol abuse among the subjects, and a 20-question cocaine pattern profile was used specifically to assess the route and temporal and quantitative patterns of cocaine abuse. We determined admission symptoms with a 22-item admission symptom checklist that included hallucinations, delusions, suicidal/homicidal ideation, and violent behavior, among others. Data from the emergency room admission sheet, as well as the patient's self-report, were included in completing the admission checklist. A 50-item cocaine symptom inventory was used to determine specific symptoms induced by use of cocaine.

All subjects were interviewed and evaluated by a research psychiatrist (G.B.) during the first 3 weeks of their hospitalization, after they had been stabilized on the ward. The patients received a complete medical evaluation and gave a complete psychiatric history. Twenty-six of the subjects had received some form of psychotropic medication (lithium, neuroleptics, antidepressants, anticholinergics, methadone) during hospitalization prior to the interview.

RESULTS

Demographic analysis of the 40-patient sample showed a sex distribution of 29 men (73%) and 11 women (28%). The mean±SD age of the subjects was 26.85±5.76 years (range=18–39). The racial distribution was 24 black, 11 white, and five Hispanic. Twenty-eight subjects were single, five were separated, two were divorced, two were married, and three were in common-law living arrangements. Earned income ranged from 0 (N=18) to $30,000 (N=1); 13 (33%) of the subjects were receiving public assistance. Eighteen (45%) of the subjects were undomiciled and only 10 (25%) were living in their own apartments. Twenty-five (63%) of the subjects were high school dropouts, and only two (5%) had graduated from college. Twenty-six (65%) had histories of at least one incarceration, and eight subjects (20%) had had more than two incarcerations.

Seven (18%) of the subjects reported previous dependence on alcohol, four (10%) previous dependence on opiates, and four (10%) previous dependence on marijuana. Thirty-four (85%) smoked cigarettes. Five (13%) of the subjects had histories of intravenous drug abuse and two (5%) were currently on a methadone maintenance regimen. Nine (23%) had previously been in a therapeutic community.

Patterns of Abuse

The route of administration was freebasing for 35 (88%) of the sample, intravenous for three (8%), and intranasal for two (5%). The mean±SD age at first use was 20.09±4.64 years for the intranasal route and 24.28±5.95 for freebasing. The mean±SD market value of the cocaine used was reported as $463.63±$491.72 (range=0–$2,500) during the week before admission, $428.00±$316.72 (range=$120–$1,500) weekly during the previous month, and $338.25±$233.50 per week during the previous year. Mean days per week of consumption were 4.50±2.76, 4.98±1.83, and 4.18±1.58 during the previous week, month, and year, respectively. Eighteen (45%) of the subjects were using crack daily the week before admission, and 24 (60%) had used it at least 5 days during the week before admission. The mean±SD estimated time interval between the last dose and entering the emergency room was 54.23±66.36 hours.

Diagnostic Analysis

The diagnostic spectrum with regard to *DSM-III-R* axis I and II comorbidity showed 17 (43%) cluster B personality disorders, 13 (33%) schizophrenic disorders, and five (13%) affective disorders. The schizophrenic subjects included 11 with chronic schizophrenia and two with schizoaffective disorder. The subjects with affective disorders included two with bipolar disorder, one with major depression, one with cyclothymia, and one with dysthymia. Of the subjects with cluster B personality disorders, 11 fulfilled the criteria for antisocial personality and six for borderline personality; two patients had schizotypal personality (cluster A). Three subjects had no other concurrent *DSM-III-R* axis I or II psychiatric diagnosis.

Subjects with the schizophrenic syndrome had used less cocaine the week before admission (mean±SD dollar value=$138.46±$129.61) than the personality disorder subjects ($710.29±$545.80) (t=−4.17, df=18.31, p<0.001), and they had used it less frequently during that week (2.54±2.33 days and 6.18±1.55 days, respectively) (t=−4.86, df=19.79, p<0.001). The schizophrenic subjects had also used less cocaine per week during the past month ($278.46±$240.03) than the personality disorder subjects ($555.88±$356.14) (t=−2.54, df=27.65, p<0.05) and during the past year ($217.69±$129.69 and $367.65±$216.46, respectively) (t=−2.36, df=26.70, p<0.05). The mean±SD elapsed time from last cocaine dose to emergency room admission was 85.40±73.56 hours for the schizophrenic subjects and 16.73±19.85 hours for the personality disorder subjects (t=2.86, df=10.19, p<0.05). The mean±SD age at first intranasal use was 22.70±4.27 years for the schizophrenic subjects and 18.33±3.37 years for the personality disorder subjects (t=2.72, df=16.24, $p<0.05$); first freebasing was at 26.92±6.22 years for the schizophrenic subjects and 21.88±5.77 years for the subjects with personality disorders (t=2.27, df=24.88, $p<0.05$).

Symptoms at Admission

At admission there was a high frequency of depression, suicidal ideation, paranoia, anxiety, auditory hallucinations, and loose associations (see table 1). Grandiose and bizarre delusions occurred in very low frequencies. Olfactory and gustatory hallucinations were not found in any of the subjects, and tactile hallucinations were recorded for only one schizophrenic subject. The schizophrenic subjects had a significantly higher frequency of auditory hallucinations than the personality disorder subjects did. Loose associations ranked high among the schizophrenic subjects but not among the personality disorder subjects (table 1).

On the cocaine-induced symptom inventory, subjects gave a frequency rating of 0 (never) to 5 (always) for 25 symptoms that they recalled experiencing 1) during cocaine intoxication and 2) 72 hours later (withdrawal phase). The data showed high mean±SD ratings for euphoria (4.70±1.02), paranoia (2.48±1.94), hyperactivity (2.40±2.10), orgasmic excitement (2.55±2.18), good taste in the mouth (2.28±2.00), and anxiety (1.93±1.89) during intoxication and high scores for depression (3.28±2.05), fatigue (3.20±2.00), anger (1.68±1.72), anxiety (1.65±1.67), and suicidal ideation (1.53±1.28) 72 hours after intoxication. Auditory hallucinations were also reported by many during intoxication (1.45±1.78), but there was no significant difference between the schizophrenic and personality disorder subjects on this item. Other kinds of hallucinations were reported at very low frequencies (<0.63) during both phases by both groups. Also, violent behavior was reported at low frequencies (<0.36) during the intoxication and withdrawal phases. Cocaine dreams, both pleasant (1.58±1.69) and bad (1.55±1.68), were reported commonly during the withdrawal phase, but no significant differences were found between the schizophrenic and personality disorder subjects on this item.

TABLE 1. Symptoms at Hospital Admission of 40 Cocaine-Dependent Psychiatric Patients and of the Subgroups With the Two Most Prevalent Diagnoses

Symptom	Total Group of Patients (N=40)		Schizophrenic Patients (N=13)		*DSM-III-R* Cluster B Personality Disorder Patients (N=17)	
	N	%	N	%	N	%
Depression	30	75	9	69	14	82
Suicidal ideation	27	68	7	54	13	76
Homicidal ideation	3	8	1	8	2	12
Violence	6	15	3	23	3	18
Paranoia	25	63	10	77	8	47
Auditory hallucinations	19	48	10	77[a]	5	29[a]
Visual hallucinations	3	8	1	8	1	6
Panic attack	7	18	4	31	1	6
Loose associations	16	40	12	92[b]	1	6[b]
Racing thoughts	4	10	1	8	0	0
Grandiose delusions	1	3	0	0	0	0
Bizarre delusions	2	5	2	15	0	0

[a] Significant difference between the schizophrenic and personality disorder patients ($\chi^2=6.65$, df=1, $p<0.01$).

[b] Significant difference between the schizophrenic and personality disorder patients ($\chi^2=22.41$, df=1, $p<0.001$).

DISCUSSION

Our analysis of 40 psychiatric inpatients who met the *DSM-III-R* criteria for cocaine dependence showed that approximately 88% of the patients were dependent on cocaine freebase "crack." The demographic data of this sample are consistent with the ominous pattern of increasing prevalence of cocaine abuse and dependence among the population with lower socioeconomic status, as recently elucidated (5). The majority of the patients in our sample were poor, belonged to ethnic minorities, were high school dropouts, and had criminal records, and a large percentage were undomiciled or receiving public assistance. The catchment area of the public hospital where our subjects were patients encompasses a large proportion of New York City. Because most of the patients who are admitted are poor, their dependency on cocaine is usually likely to lead to incarceration, homelessness, or the use of all their financial resources to buy cocaine. The difficulty in diagnosing antisocial personality disorder in the cocaine-abusing or cocaine-dependent population has been the subject of ongoing scientific debate (6).

The diagnostic spectrum of this sample revealed a high percentage of severe personality disorders (40%), which is consistent with findings in earlier studies (2, 7) and supports the theory that drug abuse may be an element of a broader behavioral phenomenon characteristic of antisocial personality (8). In our sample there was also a high percentage of schizophrenic patients, which reflects to some degree the prevalence of this disorder in the psychiatric population at this hospital: about 46%, according to emergency room admissions statistics (A. Hardesty, personal communication, March 17, 1989). This is also consistent, however, with an earlier study which reported significant cocaine abuse among schizophrenic patients (9) and another which suggested that a disproportionate number of schizophrenic patients or patients with antisocial personalities are among those who develop stimulant psychosis (10). Affective disorders were not overrepresented in our sample as had been the case in some previous studies (2, 11). However, the symptoms experienced while "crashing" from cocaine and those leading to admission were very frequently depression and suicidal ideation in patients of all diagnostic categories, including schizophrenia.

Symptoms of cocaine abusers at hospital admission have been previously described (12, 13), and a high prevalence of aggressive or psychotic behavior and elevated MMPI scores has been shown. In the analysis of admission symptoms for our sample, a comparison of the schizophrenic and personality disorder subjects showed a high frequency of depression, suicidal ideation, and paranoia for both groups and a high frequency of loose associations and auditory hallucinations for the schizophrenic group, as would be expected. Outwardly directed violence occurred in approximately one-fifth of cases in both groups. In this cohort, auditory hallucinations were reported at admission by 48%, including 29% of the subjects with personality disorders. Visual and tactile hallucinations at admission, however, were reported by only 8% and 6% of the subjects, respectively, although a previous study (14) described them as occurring more frequently than auditory hallucinations during cocaine intoxication. Whether these differences could be related more directly to the nature of our sample or to the specific properties of crack (in contrast to cocaine hydrochloride) is a question that requires further study.

Temporal and quantitative patterns of cocaine abuse have been thoroughly investigated in longitudinal studies (15), but no comparative data on patterns among different psychiatric diagnostic groups are currently available. In our study, the personality disorder subjects tended to have used more cocaine during the week, month, and year before admission and began using it at an earlier age. The patients with personality disorders also used cocaine more frequently in the week before hospitalization. The schizophrenic subjects were admitted to the psychiatric emergency room a significantly longer time after their last cocaine dose. These findings may indicate that crack is less accessible to schizophrenic persons because of their social disadvantage and their consequent diminished resourcefulness, or they may be inherently related to specific cocaine abuse patterns associated with schizophrenic disorder.

Psychiatric symptoms related to periods of intoxication and withdrawal vary widely according not only to the route, dose, intensity, and temporal course of cocaine binges but also according to the social context and the individual's premorbid psychopathology (10, 11, 16). Steps have been taken to categorize phases of intoxication and withdrawal in relation to symptoms (11) and to describe a dose-dependent progression of symptoms according to long-term clinical course (17). The analysis of our data from the cocaine-induced symptom scale shows a wide range of individual variation with regard to subjective reports about intoxication and withdrawal phases and few significant differences between the two major diagnostic groups. For example, in response to the question on orgasmic excitement during intoxication (frequently reported by cocaine abusers), five of the 17 subjects with cluster B personality disorders reported that they always experienced orgasmic excitement during intoxication, while six of the 17 reported that they never did so, and four of the 13 schizophrenic subjects reported always experiencing orgasmic excitement during intoxication, while six of the 13 reported never experiencing it.

The assessment, classification, and treatment of cocaine-dependent patients with coexisting psychiatric or personality disorders is a complicated problem that is the subject of ongoing scientific research (6, 18, 19). The relation between cocaine and its induced affective and cognitive symptoms is often ambiguous and difficult to ascertain. This problem contributes greatly to the deceptive, unpredictable, and dangerous nature of cocaine dependence. An illusion of control and denial of the severity of the disorder are prevalent among cocaine users and are perhaps the most serious and challenging clinical problems in the rehabilitation of cocaine-dependent patients. The lack of clarity about the relation between induced symptoms and cocaine use may be an even greater concern with respect to the schizophrenic population, who were more dependent and more impaired at lower doses of cocaine in our sample. The data obtained from this study demonstrate the need for multidimensional treatment of cocaine/crack dependence in our inner-city hospitals, including biological, pharmacological, psychological, and social interventions, because the overwhelming majority of these patients have coexisting psychopathology and chaotic psychosocial environments.

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Dissociative Experiences in the General Population

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The Dissociative Experiences Scale was administered to a random sample of 1,055 adults in the city of Winnipeg. Results showed that scale scores did not differ between men and women and were not influenced by income, employment status, education, place of birth, religious affiliation, or number of persons in the respondent's household. Dissociative experiences are common in the general population and decline with age. The findings suggest that dissociative disorders may also be common in the general population.

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During the 1980s there was a rapid increase in the diagnosis, treatment, and study of dissociative disorders, especially of multiple personality disorder (1–5). Several studies of a case-finding nature have suggested that dissociative disorders may be more common in clinical populations than previously suspected (6–8). High rates of dissociative disorders have been noted in preliminary screening of prostitutes and exotic dancers (9) and male sex offenders (10). However, to our knowledge there have been no systematic, large-scale studies of the prevalence of dissociation in the general population.

In the last few years three instruments for the self-report measurement of dissociation have been published (5, 11–14). One of these, the Dissociative Experiences Scale, has been subjected to a replication study (12). Thus, it has just recently become possible to determine the prevalence of dissociative experiences in the general population.

The present study provides the first findings, based on the Dissociative Experiences Scale, on the prevalence of dissociative experiences in the general population. The text of the scale, which appeared as an appendix to the original article on its validity and reliability (11), provides an operationalized definition of dissociative experiences. Such experiences include amnesia, depersonalization, a sense of being more than one person, ability to block out pain, and auditory hallucinations. Dissociative experiences are not necessarily pathological; like anxiety or depressive symptoms, they become symptoms of a psychiatric disorder when they cause marked distress and interfere with functioning.

METHOD

Procedure

Sampling. The study was conducted in Winnipeg, a city with a greater metropolitan area population of 650,000 people. On the basis of 1986 census data, a total of 233 neighborhoods were identified in the city. In accordance with standard sampling procedures recommended by Statistics Canada, 88 neighborhoods were not included in the sampling. These were neighborhoods with less than 250 residents. While they represented 38% of the neighborhoods, their population total was only 1.2% of the city population.

The sampling procedure was a three-stage, stratified random sample. First a random cluster sample of 23 neighborhoods, which represented the socioeconomic spectrum of the city, was drawn. The cluster sample was used in order to save time and money in the field work. After selection of neighborhoods, a random sample of households in each neighborhood was drawn, by using a directory that listed all addresses in the city. Households were drawn from each neighborhood in proportion to the population of the neighborhood. Finally, each household was randomized with respect to the gender of the respondent. Respondents had to be 18 years of age or older. In addition, a random sample of 400 alternative addresses was drawn up to replace respondents if necessary; this sample resulted in a replacement pool for each neighborhood equal to 25% of the households sampled in that neighborhood. Ethical approval for the study had been obtained from the Faculty Committee on the Use of Human Subjects in Research, Faculty of Medicine, University of Manitoba.

Interviewing. When an individual at a given household answered the door, that individual became the only eligible respondent in the household if he or she was of the assigned gender and over 18 years of age. No substitution of another person of the same gender was allowed. If there was no person of the specified gender living in the household, then the respondent

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became the person who answered the door, as long as that person was 18 or older. If a person not of the assigned gender answered the door, but there were eligible persons of the assigned gender living in the household, the person who answered the door was asked to choose a respondent from the pool of eligible respondents in the household. Only the first person so chosen was eligible to be the respondent for that household.

Instrument

The Dissociative Experiences Scale is a 28-item, self-report instrument for the measurement of dissociative experiences. It has a test-retest reliability of 0.84 and good split-half reliability and can discriminate subjects with multiple personality disorder from other diagnostic groups and normal control subjects (11, 12). It is not a diagnostic instrument. The scale takes about 10 minutes to complete.

The scale was called the Dissociative Experiences Scale rather than the Dissociative Symptoms Scale in order to normalize the questions. The wording of the questions was chosen for the same reason. The scale provides an operationalized definition of dissociation. As for anxiety or depression, a given dissociative experience becomes a symptom based on severity, degree of subjective distress that it causes, sociocultural context, duration, association with other symptoms, and degree of disruption to function. The scale does not measure all of these factors.

The interview questionnaire gathered data on the age, sex, education, religion, income, and ethnic background of the respondents. In addition, it inquired about the number of individuals under and over age 18 in the household, the total household income, and the ethnic background and birthplace of the respondents' parents. The demographic questions were worded in the same way as in the Winnipeg Area Study, a general population survey conducted annually in Winnipeg since 1981 on a variety of topics (15).

Data Analysis

Items on the Dissociative Experiences Scale were scored according to the instructions of Bernstein and Putnam (11). Demographic data were coded by using the code book of the Winnipeg Area Study with regard to religion, ethnic background, and income levels. Further information on the coding of responses is available from the first author.

A descriptive analysis was conducted. Overall response rates, number of addresses replaced, and reasons for replacement were tabulated. Frequency distributions of responses to each of the scale and demographic questions for the entire sample were derived, as were mean values and standard deviations.

An analysis was then done to compare men and women on all variables; two-tailed t tests were used for continuous data and chi-square tests for dichotomous data.

An analysis of variance (ANOVA) was done on all variables, taking into account the effects of both age and sex. Cell means for men versus women were analyzed by t tests for given age ranges whenever there was a significant ANOVA. For this analysis age levels were 18–29, 30–39, 40–49, 50–59, 60–69, and 70 or older. In order to avoid type I errors, the Bonferroni procedure for multiple comparisons (16) was used in this analysis. Alpha was set at $p<0.05$, and the corrected significance level was $p<0.0008$.

In addition, a regression coefficient for each Dissociative Experiences Scale item and overall score was calculated separately for men and women. The equality of regression coefficients for men versus women was then tested for each scale item and for overall scale scores. Because there were no significant differences between men and women, data for these two groups were pooled and a reciprocal least squares regression was calculated for age on each scale item and overall scale score.

Finally, a Pearson correlation matrix was constructed for all variables in the study for men and women separately and for the entire sample. With the Bonferroni procedure, the significance level for these correlations was $p<0.00009$.

Comparison of Sample to Census Data

In order to determine whether the respondents were representative of the city of Winnipeg, the demographic characteristics of the respondents were compared to 1986 census data and previous Winnipeg Area Study data (15). The current sample was compared to these previous data on age distribution and income distribution by using chi-square tests; when there was a significant finding, z scores were calculated separately for each age and income level in the sample. For calculation of z scores, the average values of the four Winnipeg Area Studies were used.

RESULTS

Sample

The initial sample consisted of 1,600 households. Altogether, 289 addresses were replaced for the following reasons: household vacant (N=52), no contact after six visits (N=136), limited or no knowledge of English (N=49), and all other reasons (N=52). A total of 350 households were judged not eligible, but 61 were not replaced for the following reasons: no further replacement addresses available in that neighborhood (N=17) and time constraints (N=44). The final sample size was 1,539 households.

Of the 1,539 households there were 1,055 completed interviews (68.6%), 441 refusals (28.7%), and

TABLE 1. Ages of Respondents in the Present Random-Sample Study of Winnipeg, Four Previous Random Samples of Winnipeg, and 1986 Census Data

Age (years)	Present Study (N=1,025)[a] N	Present Study (N=1,025)[a] %	Winnipeg Area Studies (N=500–546) (%)[b]	1986 Census (N=453,455) N	1986 Census (N=453,455) %
20–24[c]	79	7.7	10.3–12.4	60,310	13.3
25–34[d]	288	28.1	24.4–31.0	114,271	25.2
35–44[e]	281	27.4	19.9–24.9	86,156	19.0
45–54	124	12.1	10.8–16.0	58,949	13.0
55–64[f]	93	9.1	8.0–12.6	58,496	12.9
65–74	88	8.6	7.0–11.4	44,892	9.9
75 or older	72	7.0	5.7–6.4	30,381	6.7

[a] Significant overall differences between the present study and the Winnipeg Area Studies (χ^2=15.57, df=6, p<0.005) and the 1986 census data (χ^2=79.76, df=6, p<0.00001).

[b] Winnipeg Area Study figures are the range of values from 1986 to 1989. The number of respondents was 521–581 per year, for a total of 2,178 over the 4 years.

[c] Significant differences between the present study and the Winnipeg Area Studies (z=2.98, p<0.01) and the 1986 census data (z=5.28, p<0.001).

[d] Significant difference between the present study and 1986 census data (z=2.13, p<0.05).

[e] Significant difference between the present study and the Winnipeg Area Studies (z=3.21, p<0.01) and the 1986 census data (z=7.00, p<0.001).

[f] Significant difference between the present study and 1986 census data (z=3.62, p<0.01).

43 unresolved (addresses at which no one could be contacted) (2.8%). Of the refusals, 390 subjects refused at the door and 12 refused by phoning the research office or returning the initial letter; 39 were rated as refusals because they lived in locked apartment buildings and the household could not be contacted. A second letter asking the householder to contact the research office was mailed to each of these 39 lockout apartment addresses, but none of the households responded.

Among the 1,055 respondents there were 609 women (58.3%) and 435 men (41.7%); gender data were missing for 11 respondents. The difference in number of men and women, compared to an expectation of 50% men and 50% women based on random sampling of gender, was significant (χ^2=29.0, df=1, p<0.0001). The mean±SD age of the women was 44.4±17.5 years and of the men, 41.6±15.4 years (t=2.64, df=1029, p<0.008). The mean age for the entire sample was 43.2±16.7 years; the median age was 43 years.

Table 1 compares the age distribution of the respondents to 1986 census data for Winnipeg and four annual Winnipeg Area Studies from 1986 to 1989. The current sample differed significantly from 1986 census data. Comparing census data and the current sample at each age level, we found significant differences for 20–24 years, 25–34 years, 35–44 years, and 55–64 years but not for the other age levels. The current sample differed significantly from the average values for the four previous Winnipeg Area Studies as well. Comparing Winnipeg Area Study data and the current sample at each age level, we found significant differences for 20–24 years and 35–44 years but not for the other age levels.

The mean individual income for the women in the sample was $16,109.73±$13,085.65 and for the men, $28,806.88±$17,243.45 (t=12.57, df=900, p<0.00001). The mean individual income for the entire sample was $21,391.76±$16,200.62. The median individual income range for the entire sample was $18,000.00–$19,999.00.

There was no significant difference between the personal income level of the respondents in the present study and those in the four annual Winnipeg Area Studies (χ^2=7.65, df=3, n.s.). The mean household income for the women was $34,670.54±$21,508.79 and for the men, $41,561.68±$21,330.13 (t=4.75, df=895, p<0.00001). The mean household income for the entire sample was $37,576.80±$21,627.14. The median range for household income was $34,000.00–$35,999.00. There was no significant difference between the household income level of our respondents and those in the four annual Winnipeg Area Studies (χ^2=6.13, df=3, n.s.).

Concerning the education of the respondents, 11.7% (N=123) had junior high school education or less, 61.3% (N=643) had at least some high school or other nonuniversity education, and 27.0% (N=283) had at least some university education. Educational data were missing for six subjects. The mean number of years of schooling in the sample was 12.8±3.6. In the Winnipeg Area Study, 9.7%–17.5% of the respondents had junior high school education or less, 53.6%–69.3% had at least some high school or other nonuniversity courses, and 18.9%–34.0% had at least some university education.

Altogether, 45.9% (N=474) of the respondents had worked full-time for the previous 12 months, compared to 51.5% in the 1989 Winnipeg Area Study. Concerning lifetime employment patterns, 74.6% (N=783) of our sample had worked primarily full-time, 11.0% (N=115) primarily part-time, and 9.0% (N=94) a combination of full- and part-time; 4.9% (N=51) had never been in the labor force. Six subjects gave a response of "other," and data were missing for six subjects.

Concerning the ethnic and religious backgrounds of the respondents, 75.9% (N=797) were born in Canada, 12.4% (N=130) in Europe, in the United States, or the U.S.S.R., and the remaining 11.7% (N=123) elsewhere. Data on place of birth were missing for five subjects. For 38.7% (N=408) both parents were born outside Canada, for 11.6% (N=120) one was born in Canada, and for 49.8% (N=516) both parents were born in Canada. Data were missing for 11 subjects.

The majority of the respondents were practicing Christians. Of the total sample, 76.1% (N=793) identified themselves as belonging to a Christian church: 27.6% (N=288) were Roman Catholic, 13.0% (N=135) belonged to the United Church of Canada, and

TABLE 2. Dissociative Experiences Scale Scores by Age for Men and Women in a Random-Sample Study of Winnipeg (N=1,055)

Age (years)	Men (N=435)[a] Mean	SD	Women (N=609)[a] Mean	SD
18–29	15.2	12.7	15.6	12.1
30–39	11.9	10.2	10.3	8.9
40–49	8.7	9.3	10.9	8.3
50–59	6.0	4.5	7.0	5.3
60–69	5.9	5.1	10.9	14.0
70 or older	9.0	7.1	6.8	6.5

[a]Gender data were not reported for 11 subjects.

9.6% (N=100) were Anglican. Of the total sample, 0.4% (N=4) identified themselves as atheists, 0.9% (N=9) as agnostics, and 11.3% (N=118) as having no religious preference or affiliation. Data on religion were missing for 13 subjects. Of the total, 29.2% (N=305) identified religion as very important to them at present, giving it a rating of 7 on a 7-point Likert-type scale; similarly, 26.4% (N=276) rated the importance of religion to them in their childhood as 7 on the 7-point scale. Data on this subject were missing for 11 subjects.

Dissociative Experiences

The mean score for the women on the Dissociative Experiences Scale was 10.8 ± 10.1 and for the men it was 10.7 ± 10.2 ($t=0.20$, $df=1042$, n.s.). The mean score for the entire sample was 10.8 ± 10.2; the median score was 7.0. Men and women differed on only two items on the scale ($p<0.002$ after application of the Bonferroni correction). These were item 9 ("Some people find that they have no memory for important events in their lives, for example, a wedding or graduation") and item 21 ("Some people sometimes find that when they are alone they talk out loud to themselves").

Men scored higher than women on item 9 (11.3 ± 20.2 versus 6.8 ± 15.5; $t=4.11$, $df=1042$, $p<0.00001$). Women scored higher on item 21 (17.5 ± 23.4 versus 11.8 ± 19.0; $t=4.19$, $df=1042$, $p<0.00001$).

There were no differences in mean Dissociative Experiences Scale scores between the sexes at each age level. The numbers of men and women at each age level were as follows: 18–29 years, 95 men and 127 women; 30–39 years, 130 men and 177 women; 40–49 years, 103 men and 107 women; 50–59 years, 38 men and 48 women; 60–69 years, 31 men and 68 women; and 70 or greater, 34 men and 73 women. Because data on age were missing for 13 subjects and on gender for 11 subjects, age and gender were both evaluated for 1,031 subjects.

Table 2 shows the mean scores on the Dissociative Experiences Scale for both sexes at different ages. Mean scores declined significantly with age in both sexes ($p<0.0008$ after application of the Bonferroni correction). Men 18–29 years old scored significantly higher than men 40–49, 50–59, and 60–69. Men 18–29 and 30–39 scored significantly higher than women 30–39, 40–49, 50–59, 60–69, and 70 or older. Women 18–29 scored significantly higher than women of all other ages and significantly higher than men of all ages. All comparisons were significant at $p<0.01$.

TABLE 3. Frequency Distribution of Dissociative Experiences Scale Scores in a Random-Sample Study of Winnipeg (N=1,055)

Score	Subjects N	%	Cumulative N	%
0	70	6.6	70	6.6
1–5	334	31.7	404	38.3
6–10	272	25.8	676	64.1
11–15	152	14.4	828	78.5
16–20	92	8.7	920	87.2
21–25	46	4.4	966	91.6
26–30	36	3.4	1,002	95.0
31–35	17	1.6	1,019	96.6
36–40	15	1.4	1,034	98.0
41–45	9	0.9	1,043	98.9
46–50	4	0.4	1,047	99.3
51 or greater	8	0.8	1,055	100.0

There were no significant differences between men and women in regression coefficients on any of the 28 scale items or overall scale scores. The data were pooled, and a reciprocal least squares regression showed that overall scale scores declined significantly with age in a nonlinear fashion.

There was considerable variation in the frequency distribution of responses to the individual scale items. For instance, 29.0% (N=306) of the sample indicated that they experienced item 2 ("Some people find that sometimes they are listening to someone talk and they suddenly realize that they did not hear part or all of what was said") more than 30% of the time, whereas only 1.2% (N=13) experienced item 11 ("Some people have the experience of looking in a mirror and not recognizing themselves") more than 30% of the time.

Of note was the frequency distribution of responses to item 27 ("Some people sometimes find that they hear voices inside their head which tell them to do things or comment on things they are doing"). Of the sample, 26.0% (N=274) had heard voices at some time, 7.3% (N=77) had heard voices 25% of the time or more, and 5.0% (N=53) had heard voices more than 30% of the time. Subjects completing the Dissociative Experiences Scale are instructed that they are to endorse experiences that happen only while they are not under the influence of drugs or alcohol.

Table 3 presents a frequency distribution of average scale scores in the sample.

The results of the Pearson correlations indicated that in the overall sample there was no significant correlation between scores and number of individuals under age 18 in the household, number of individuals over age 18 in the household, number of months the respondent had worked full-time and part-time in the previous year, years of schooling, importance of religion in childhood or at present, or individual or household income.

Age correlated significantly with scale score among women ($r=-0.22$, $N=600$, $p<0.00001$), among men ($r=-0.26$, $N=431$, $p<0.00001$), and in the overall sample ($r=-0.23$, $N=1042$, $p<0.00001$). All 28 scale items correlated with overall scale scores at $p<0.00001$ among men and women and in the overall sample.

Results of t tests showed that place of birth had a significant effect on scale scores. Persons born in Europe, the U.S.S.R., or the United States scored lower than those born in Canada ($t=3.85$, $df=2$, $p<0.0001$) and elsewhere ($t=4.66$, $df=2$, $p<0.00001$). However, when these groups were analyzed by age, it was apparent that the lower scores among respondents born in Europe, the U.S.S.R., and the United States were due to the significantly larger number of older respondents in this group.

DISCUSSION

The data from this study provide the first information on dissociative experiences in the general population. Comparison of the demographic characteristics of the sample of 1,055 respondents to 1986 census data and previous random samples of the population indicates that our sample was representative of the city of Winnipeg in terms of education and personal and household income. There were significantly more women than men in the sample, but since men and women did not differ in average scale scores, the overrepresentation of women did not skew the findings.

There were significant differences in age distribution between the current sample and both census data and previous random samples of the population. These differences were detected because of the large sample sizes and power of the statistics used. Although they might limit the generalizability of the findings to some degree, it is evident from table 1 that the sample was similar to the general population in age distribution. We do not think that these statistical differences are of major conceptual importance.

Winnipeg is a midwestern Canadian city with a greater metropolitan area population of 650,000. Caution is required in generalizing the findings to all other urban centers in North America. However, overall scores on the Dissociative Experiences Scale did not differ between men and women, nor was there a significant correlation between overall scale score and individual or household income, education, number of individuals under 18 or over 18 years of age in the household, place of birth, or importance of religion to the respondent in childhood and at present. Therefore, it is likely that the norms for Winnipeg can be generalized to much of urban North America.

The fact that all 28 scale items correlated with overall scores at $p<0.00001$ indicates that the instrument is an internally coherent measure of a related group of experiences. The Dissociative Experiences Scale has demonstrated validity and reliability (11, 12), and the observation that group median scores on the scale differentiate subjects with a number of psychiatric disorders from each other and from normal control subjects has been replicated (12). High scale scores are suggestive but not diagnostic of a dissociative disorder. The information derived from the Dissociative Experiences Scale appears to be valid and meaningful. The design of the study and the phrasing of scale items make it unlikely that observer bias or demand characteristics had any significant effect on responses.

Several observations can be made. In our study, dissociative experiences were equally common in men and women at all age levels from 18 years onward. Men and women differed on only two items on the scale. Women may talk out loud to themselves more than men because they spend more time alone at home in our culture. Men may forget important events such as anniversaries because of cultural reasons in North America and because of sex role stereotyping. At any rate, the differences between men and women on these two items did not seem crucial to us or of obvious conceptual importance.

Spontaneous dissociative experiences decline with age in the general population and appear to level off in the fourth decade. A previous nonrandom sample of 168 normal adolescents showed that scores on the Dissociative Experiences Scale declined significantly from age 12 to age 14 (17). In that study 12-year-olds had a median score of 20.2 and 14-year-olds a median score of 14.9.

In assessing the Dissociative Experiences Scale score of an individual, it is important to take age norms into account, including the smaller standard deviations in older persons. It appears that dissociative experiences in the general population decline with age on a curve roughly similar to the decline in hypnotizability (18–21). The relationship between dissociation and hypnotizability is discussed extensively in the literature on dissociative disorders (4, 5, 22). Dissociative experiences may be the spontaneous trait expressions of a state referred to as hypnotizability, or hypnotizability and dissociativeness might be thought of as closely linked to each other. Our data suggest that the two phenomena covary in the general population.

The degree of spontaneous dissociation in the general population is independent of all major socioeconomic factors other than age, including income, education, employment status, household size, importance of religion, and place of birth. This suggests that at least a component of spontaneous dissociation in the general population is due to endogenous factors rather than psychosocial experience. Any psychosocial factors stimulating dissociation appear to be distributed throughout the general population independently of the socioeconomic factors measured in this study.

The psychosocial factor most clearly associated with multiple personality disorder, the most complex dissociative disorder, is severe, chronic child abuse (4, 5, 23, 24). If Dissociative Experiences Scale scores are sensitive to the distribution of child abuse in the general population, one can infer from the data that sexual and physical abuse of children affects all socioeconomic strata equally. This possibility, which has not been addressed by the present data, will be investigated in the second phase of the study, in which the respondents will be interviewed with the Dissociative Disorders Interview Schedule (14) by interviewers blind to their responses to the first interview.

The Dissociative Disorders Interview Schedule makes a detailed inquiry about child abuse and a range of dissociative symptoms and makes *DSM-III-R* diagnoses of somatization disorder, major depressive episode, borderline personality disorder, and all of the dissociative disorders (5, 9, 14, 25).

The findings of this study indicate that dissociative experiences are common in the general population: 5.0% of the general population scored above 30 on the Dissociative Experiences Scale, 8.4% above 25, and 12.8% above 20. Scores above 20 are indicative of a substantial number of dissociative experiences in an individual's life. The question arises, When are dissociative experiences pathological? Dissociative Experiences Scale scores by themselves cannot answer this question. A definitive study would require coadministration of the Dissociative Experiences Scale and a diagnostic interview, such as the Dissociative Disorders Interview Schedule (14) or the Structured Clinical Interview for DSM-III-R Dissociative Disorders (26), to a random sample of the general population.

In clinical studies scores above 30 on the Dissociative Experiences Scale are associated with a high likelihood of posttraumatic stress disorder or multiple personality disorder (11, 12, 25). In a sample of 82 patients with multiple personality disorder, for instance, the mean Dissociative Experiences Scale score was 41.4±20.0 (range=1.3–83.6) (27).

Findings from clinical studies using the Dissociative Experiences Scale, combined with the present data, lead to a tentative prediction that the dissociative disorders, including multiple personality disorder, may be relatively common, with a prevalence that may be in the range of 5%–10% of the general population. If this prediction is borne out, it will be clear that a major form of psychopathology in North America has been almost entirely missed by most mental health professionals. Since dissociative experiences are common in the general population, we suspect that dissociative symptoms may occur in a wide range of psychiatric disorders, just as anxiety and depression can be components of many different diagnostic entities.

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Should Psychiatrists Administer Anesthesia for ECT?

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Whether psychiatrists are qualified to give anesthesia for ECT is controversial. At the authors' hospital, over a 9-year period ECT resulted in no mortality and minimal morbidity; in 98.8% of the treatments, anesthesia was given by psychiatrists. The average nursing time required for cases in which anesthesiologists administered anesthetic was longer than that for psychiatrists' cases. This difference may be related to succinylcholine dose and efficacy of ECT. The authors' surveys indicated that psychiatrists and anesthesiologists have differing opinions on whether psychiatrists should administer anesthesia for ECT and that few psychiatry residency programs which teach ECT provide training in anesthesia.

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> Now who will stand on either hand
> And keep the bridge with me?
>
> —T.B. Macaulay, "Horatius"

The question of whether or not psychiatrists should administer anesthesia for ECT or routinely use anesthesiologists is being hotly debated in the Houston area. The 1978 APA task force report on ECT (1), while providing detailed data on education, training, techniques of administration, research, social implications, legal issues, and ethical aspects of ECT, carefully avoided the issue of who exactly should administer the anesthesia. The newest APA task force report on ECT (2) emphasizes the therapeutic value and safety of the treatment but also steers away from the controversy. In 1979 Fink (3) expressed uncertainty about whether an anesthesiologist or a psychiatrist is the most appropriate physician to deliver the anesthesia. Subsequently, he asserted that anesthesiologists are of considerable help and may be required for complex cases (4). He supported the role of psychiatrists in giving anesthesia for ECT if medical boards, regulatory agencies, and certifying boards endorse their training and skills. In a survey of ECT in Great Britain (5), it was found that 22% of the treatment facilities responding always used an anesthesiologist, 43% intermittently used specialist services, and 25% used general practitioners. In South Africa the use of anesthesia and ECT requires the presence of two licensed physicians, one to administer anesthesia, the other to provide the electrotherapy. A paper from the Royal Adelaide Hospital, Australia (6), addressed the question of whether a single operator giving both anesthesia and ECT can devote full attention to patient care.

Memorial Southwest Hospital in Houston provides comprehensive medical and surgical care and includes a 68-bed accredited psychiatric unit. ECT has been available at the hospital for 40 years. Until recently, psychiatrists on the staff who were credentialed to administer anesthesia for ECT on the basis of knowledge, training, and experience were free to either give their own anesthesia or use the services of an anesthesiologist. On Sept. 1, 1989, the hospital mandated that all anesthesia for ECT be provided by the department of anesthesiology. The hospital permitted psychiatrists currently administering courses of anesthesia and ECT to complete these treatments before fully implementing the new ruling.

Apart from adding substantially to the cost of ECT by mandating use of anesthesiologists, denying psychiatrists this privilege adds to the already restrictive difficulties of rendering ECT. Negative lay and legal attitudes toward ECT are exemplified by movies such as "One Flew Over the Cuckoo's Nest" (7) and California Assembly Bill 1032, which describes ECT as experimental, like psychosurgery, in spite of numerous studies, some controlled, finding ECT superior to chemotherapy in the treatment of depression (8). Technical progress, such as the use of EEG-monitored seizures, has been overshadowed by cumbersome legislative and political restrictions (9).

METHOD

To determine whether or not there are valid scientific reasons for anesthesiologists to exclusively provide anesthesia for ECT, we reviewed all ECT given at Memorial Southwest Hospital from Jan. 1, 1981, until Oct. 31, 1989. We looked at number of treatments given, number of courses of treatment, average num-

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TABLE 1. Number of ECTs Performed in a Houston Hospital From 1981 to 1989

	ECTs				
Year	Total	Inpatients	Outpatients	Courses	Treatments per Course
1981	1,159	862	297	121	9.58
1982	1,212	1,035	177	113	10.73
1983	963	748	215	111	8.68
1984	998	813	185	118	8.46
1985	943	734	209	111	8.50
1986	828	632	196	84	9.86
1987	736	516	220	82	8.98
1988	699	527	172	76	9.20
1989[a]	623	453	170	68	9.16
Total	8,161	6,320	1,841	884	9.23

[a] January 1 to October 31.

ber of treatments per course, morbidity and mortality rates, and number of treatments for which anesthesia was given by psychiatrists and by anesthesiologists. We determined the total amount of time allocated by the director of nursing services for nursing assistance with ECT and compared the time required when anesthesia was administered by psychiatrists to the time required when anesthesia was given by anesthesiologists.

We also surveyed random samples of 100 psychiatrists and 100 anesthesiologists with practices in Harris County before and after providing them with our review data on morbidity and mortality. We asked whether or not psychiatrists with adequate training were qualified to administer anesthesia for ECT. Since an increasing number of psychiatric units operate as free-standing psychiatric hospitals unattached to medical and surgical hospitals, we asked anesthesiologists whether they would be willing to provide anesthesia for ECT at free-standing psychiatric facilities.

We asked the medical directors of 100 training programs for adult psychiatry whether ECT and anesthesia for ECT were taught at their facilities. Finally, we solicited information from psychiatrists practicing at Memorial Southwest Hospital who used ECT during the period of this study about their education and training in ECT.

RESULTS

Hospital Experience

In table 1, we show a total of 8,161 ECT treatments given from the beginning of 1981 until the end of October 1989 to inpatients and outpatients, number of courses of treatment, and average number of treatments per course. For 8,061 treatments anesthesia was administered by psychiatrists, and for 90 treatments it was given by anesthesiologists. In 10 cases anesthesia was administered by psychiatrists with supervision by anesthesiologists, and for the purposes of our study we have not assigned these cases to either psychiatrists or anesthesiologists. Regardless of whether anesthesia was administered by psychiatrists or anesthesiologists, there were no fatalities, no fractures, no aspiration pneumonias, and no post-ECT atelectases. Indeed, since 1973, 17,500 ECT treatments have been done at the hospital and there have been no fatalities. During three treatments in which anesthesia was administered by psychiatrists, individuals with poor dental condition suffered broken teeth; in another case, the patient vomited under anesthesia, but suction effectively prevented aspiration. Surprisingly, in three cases involving anesthesiologists, bradycardia (pulse below 42 beats/min) occurred in patients not given pre-ECT atropine or glycopyrrolate.

We randomly selected two calendar months during 1989 when all anesthesia for ECT was administered either by psychiatrists or by anesthesiologists and determined the average nurse assistance time required per case. For May 1989, when all anesthesia for ECT was given by psychiatrists, the average nurse assistance time per case was 37.9 minutes. For October 1989, following the mandatory implementation of the new ruling that all anesthesia for ECT must be administered by anesthesiologists, the average nursing time per case was 55.3 minutes.

Surveys

Of the 100 psychiatrists to whom we sent the initial survey, 61 responded. Of these, 38 (62%) believed that adequately trained psychiatrists should be permitted to administer anesthesia for ECT for medically stable patients. Twenty-three (38%) considered psychiatrists unqualified to administer anesthesia for ECT. Significantly, of this number, 15 (65%) did not utilize ECT in their practices. The subsequent survey, after the morbidity/mortality findings were provided to the same randomly selected 100 psychiatrists, yielded only 31 responses. Of these 31 respondents, 25 (81%) concluded that psychiatrists should be permitted to administer anesthesia for ECT; 19% (N=6) adhered to the opinion that psychiatrists should not administer ECT anesthesia.

Of the 100 randomly selected anesthesiologists, 41 responded to the first survey, before our morbidity/mortality results were made available to them. Of these, 37 (90%) believed that psychiatrists should not administer anesthesia for ECT. When the same randomly selected anesthesiologists were given the results of our morbidity and mortality findings, involving over 8,000 cases in which anesthesia was given by psychiatrists, they failed to change their opinions. Of the 40 anesthesiologists who responded to the second survey, 36 (90%) opined that psychiatrists are not competent to administer anesthesia for ECT. In response to the question about whether the anesthesiologists were willing to provide anesthesia for ECT at free-standing psychiatric facilities, 21 (53%) replied that they would not do so and 19 (48%) stated they would be willing.

In response to our inquiry about whether psychiatrists and anesthesiologists thought it was safe for a single operator to administer both the anesthesia and the ECT, 25 (81%) of 31 responding psychiatrists thought a single operator could safely provide both treatments, but 34 (85%) of 40 anesthesiologists thought it was unsafe.

Of the 100 randomly selected adult psychiatry residency training programs to which we sent surveys, 88 responded. Of these 88 programs, 72 (82%) teach ECT and 16 (18%) do not. Of the 72 programs that provide training in ECT, only six (8%) also train their residents in the administration of anesthesia for ECT.

Of 12 psychiatrists at Memorial Southwest Hospital who administered ECT during the time of this study, all had received training in anesthesia for ECT during their residencies.

DISCUSSION

A finding of no mortality and very little morbidity from more than 8,000 ECT treatments, in 98.8% of which anesthesia was administered by psychiatrists, underscores the safety of ECT anesthesia in the hands of trained psychiatrists. These findings replicate the data in four large studies over the past 18 years, in which no deaths resulted from modified ECT (10). The negative attitude of surveyed anesthesiologists toward psychiatrists administering anesthesia for ECT is not justified by our data and appears related more to professional competition than to clinical validation. Five decades ago, when ECT was given without anesthetic drugs, the mortality rate was a mere 0.06% (11). Nevertheless, isolated deaths during ECT with anesthesia have been reported (12). The mortality rate for depressed patients is higher than the age-corrected rate for the general population, even when deaths from suicide are excluded (13). Depressed patients given ECT have a mortality rate similar to the age-corrected rate for the general population (13).

Clinical psychiatry has a history of using unconsciousness-inducing modalities to treat mental illness. Twenty years before the advent of neuroleptic drugs, insulin coma therapy ameliorated acute exacerbations of schizophrenia (14). Psychiatrists using this treatment were trained in the total care of the unconscious patient, including maintenance of a patent airway, precautions against aspiration, and monitoring of neurological vital signs. The introduction of ECT in 1938 added a new dimension to psychiatric expertise in managing the unconscious patient (15, 16). The induction of an unmodified seizure in itself anesthetized the patient, necessitating ventilatory and other resuscitative care. Whereas anesthesiologists currently criticize administration of anesthesia by psychiatrists, in those days there were no dissenting voices clamoring for retraction of psychiatrists' anesthesia privileges. Ironically, the introduction of succinylcholine into ECT in 1951 preceded its use in general anesthesia (17). Of the numerous articles on anesthesia and ECT, few have been written by practicing anesthesiologists.

While it is unquestionably desirable or necessary to use an anesthesiologist in ECT for elderly or medically unstable patients, differences in ECT anesthesia technique between psychiatrists and anesthesiologists may have important and thus far insufficiently recognized influences on the efficacy of ECT. In our study, differences in allocated nursing assistance time between the two groups may reflect differences in the average doses of anesthetic drugs used. In the experience of one of us (T.P.), who has sometimes administered anesthesia for ECT himself and sometimes used anesthesiologists, anesthesiologists use similar doses of sleep-inducing agents but higher doses of succinylcholine, resulting in a longer post-ECT recovery time.

How ECT works and relieves depression and catatonic schizophrenia is unknown. A generalized seizure is thought to be necessary for an effective response (18). Clinical experience suggests that a subconvulsive stimulus may be positively harmful (19). Duration of generalized seizure activity, measured both clinically and with EEG monitoring, has been demonstrated to be a therapeutic factor in ECT (20, 21). Shorter seizures, as may occur in patients given diazepam before ECT, have less antidepressive effect (22–25). The dose of succinylcholine has been found to be inversely related to seizure duration (20). However, claims that there is a positive correlation between seizure duration and ECT efficacy have been disputed by Daniel (26), who observed that no study to date has proven such a finding without confounding the results with number of treatments given. Nevertheless, the relationship between anesthesia and efficacy of ECT remains an important issue and warrants further controlled research. The greater the antidepressive effect of an electrically induced seizure, the fewer ECT treatments are indicated, thus minimizing the cumulative impact of side effects.

Differences between the psychiatrists and anesthesiologists we surveyed in their opinions concerning the safety of a single operator's administering both anesthesia and ECT were substantial: 81% of the psychiatrists considered it safe, and 82% of the anesthesiologists held the opposite view. We believe that just as angioplasty operators use two cardiologists to provide "extra hands," the use of two psychiatrists, one to administer anesthesia and one to administer ECT, maximizes patient safety and efficacy of treatment.

We are concerned that 18% of the psychiatric residency programs surveyed do not teach ECT and that, of those which provide training in ECT, few teach the administration of anesthesia with the procedure. Such policy, in our opinion, reinforces "demedicalizing" attitudes toward psychiatrists by the rest of the medical profession. Psychiatrists are being reduced to mere assistants to anesthesiologists (27). Our study provided no facts to justify the view that only anesthesiologists are sufficiently competent to administer anesthesia for ECT. It seems significant to us that the current demedicalizing attitudes toward psychiatry are the reason why psychiatrists and not gastroenterologists, cardiologists, or dentists are being singled out as unqualified to administer anesthesia in our field. A medically trained psychiatrist should be as competent to deal with the remote possibility of cardiac arrest during ECT as a family practitioner, who might have to render emergency treatment to a patient who develops acute vagal inhibition while having an ear syringed—a possible but extremely unlikely complication.

For assurance that psychiatrists are competent to administer anesthesia for ECT, the credentialing for these privileges needs to be rigidly conducted. Evidence of knowledge and of experience during properly supervised training in the administration of anesthesia for ECT needs to be provided. Each applicant for ECT anesthesia privileges needs to provide proof of a current advanced cardiac life support certificate. In each hospital there needs to be collaboration between the department of psychiatry and the department of anesthesiology so as to assure that unified standards of anesthesia for ECT are upheld by all appropriately credentialed physicians.

The bridge between medicine and psychiatry painstakingly developed by nineteenth-century psychiatrists, such as Benjamin Rush and Isaac Ray in the United States (28), Kraepelin in Europe (29), and Mayer-Gross in Britain (30), is being undermined by negative attitudes toward our medical identity, as exemplified in this study by the views of anesthesiologists and division in our own ranks concerning the use of ECT. Our profession must recognize that comprehensive training and experience in all somatic diagnostic tests and treatments alleviating mental illness, in addition to therapeutic alliances and psychotherapeutic skills, are fundamental to the survival of psychiatry as a medical discipline separate from psychology, sociology, and philosophy. Strengthening our medical identity will, we hope, reverse the trend of nonacceptance of psychiatrists as anesthetists, thus permitting cost-effective quality ECT to be practiced.

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Psychiatry Takes to the Streets: The New York City Initiative for the Homeless Mentally Ill

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The authors describe New York City's program to remove seriously mentally ill homeless people from the streets to a public hospital. They report on the 298 patients hospitalized during the first year of this program. Most of the patients were male (66%), single (77%), and from outside of New York City (79%) and claimed a history of previous psychiatric hospitalization (92%) and that they had been homeless for more than 1 year (66%). Most of the patients suffered from schizophrenia (80%) and had additional medical diagnoses (73%). Follow-up contact with the patients 2 years after initiation of the program revealed that 55% of the patients either were living in a community setting or were under institutional care.

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One of the most frequently and vehemently debated side effects of more than three decades of deinstitutionalization policies is the upsurge in the numbers of chronically mentally ill individuals who are homeless in our city streets (1–8). Although the exact relationship between deinstitutionalization and the increase in homeless mentally ill individuals continues to be a subject of controversy (9–11), it is now apparent that a substantial proportion of the homeless mentally ill are men and women who before deinstitutionalization would have been residents of state mental hospitals (12–14).

In recent years, in response to pressure from the media, advocacy groups, and mental health professionals, new reparative programs are emerging to reach the many deinstitutionalized and never-institutionalized seriously mentally ill individuals who remain untreated in our urban communities (15–22). At the same time, public outrage about the inhumane quality of life for the seriously mentally ill who refuse care has brought renewed pressure to relax the laws on involuntary psychiatric treatment (23–25). In the process, the emergency rooms of readily available public general hospitals have become the place of first resort for seriously mentally ill indigent patients, as well as convenient settings for policy makers attempting to provide shelter and treatment for this population (26–30).

On October 28, 1987, the mayor of New York City instituted an unprecedented program to address the health care needs of homeless individuals living on the street who were severely mentally ill but who consistently resisted support and treatment (31). The new program required the removal from the streets to a public hospital of mentally ill homeless individuals who were neglecting their essential needs for food, clothing, shelter, and medical care and who, by reason of their mental illness, were at risk of physical harm within the reasonably foreseeable future (32). Since its announcement, the New York City program has received extraordinary local and national attention, and many urban centers, similarly affected by the overwhelming problems of caring for the homeless mentally ill, have closely monitored the program's development (33–39).

The purpose of this paper is to describe the New York City program, present data on the demographic and clinical characteristics of the patients hospitalized during the first year of the program, and report on the location of these patients 2 years after its implementation. Although the existing literature on the homeless mentally ill is extensive, there have been few studies of specific treatment strategies directed toward this population.

PROGRAM DESCRIPTION

The evaluation of homeless mentally ill individuals in the streets is the responsibility of the Homeless Emergency Liaison Project (Project HELP). This mobile unit is staffed by psychiatrists, nurses, and social

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workers. The psychiatrists are empowered to order the police to transport persons who meet the program's criteria (i.e., mental illness, need of hospital care, and risk of physical harm within the reasonably foreseeable future due to neglect of essential needs) involuntarily to Bellevue Hospital's emergency room for further evaluation and, if indicated, hospitalization. Project HELP responds to referrals from the police, concerned citizens, social agencies, and psychosocial outreach teams through a publicized telephone help line. During the time of this study, Project HELP's service area included the entire borough of Manhattan, where the great majority of the homeless live.

After the patients are evaluated in Bellevue Hospital's emergency room, if indicated, they are admitted to a specialized 28-bed, short-term intensive care psychiatric unit. The unit has enhanced psychiatric and medical staff recruited specifically for the program. Once the specialized unit is at capacity, additional Project HELP patients are sent to other psychiatric units of the hospital. Legal representation is available to these patients in accordance with the state's mental hygiene law. Each patient is examined by a psychiatrist on the street, another psychiatrist in the emergency room, and a third psychiatrist within 48 hours of admission to the inpatient unit. The three psychiatrists have to concur independently as to the need for involuntary hospitalization in order for the patient to remain in the hospital against his or her will.

Another program component is a 70-bed inpatient unit at Creedmoor Psychiatric Center, a long-term-care state facility located in the borough of Queens. This service is for patients who are deemed in need of extended institutional psychiatric care after hospitalization at Bellevue Hospital. Also, the city established a 30-bed rehabilitation transitional living program, staffed by Bellevue Hospital clinicians, at a municipal shelter for men. This setting serves as a temporary discharge alternative for improved patients for whom no other community setting is readily available. In addition to these program-specific aftercare resources, patients also have access to existing community residences, adult homes, health-related facilities, and ambulatory aftercare supports.

Other elements of the program consist of the various means used to monitor these patients and the services provided to them, such as a computerized tracking system. In addition, regular interagency meetings are held to share clinical information, to resolve problems, and to monitor services. Finally, a small case management program is in place both at Bellevue Hospital and at Creedmoor Psychiatric Center to facilitate patients' linkages to aftercare resources.

PATIENT CHARACTERISTICS AND SERVICES

We examined the records of the 298 mentally ill homeless individuals who, after evaluation by Project HELP in the streets, were brought to Bellevue Hospital from October 28, 1987, through October 27, 1988, the first year of the implementation of the new program. Demographic data, psychiatric histories, and data on duration of homelessness were obtained from the patients' clinical records. Psychiatric diagnoses and additional medical diagnoses (*ICD-9*) were extracted from medical records at Bellevue Hospital. Most of the patients (N=196 [65.8%]) were men, and 143 (48.0%) were white. Most were either single (N=228 [76.5%]) or separated or divorced (N=50 [16.8%]). Regardless of their marital status, 54 (18.1%) claimed to have children of their own. Their ages ranged from 16 to 80 years (mean=43, median=40). For the 178 patients who provided information regarding their education, the average level of schooling completed was the 11th grade. Of those providing such information (N=281), a large number (N=223 [79.4%]) gave a location other than New York City, including foreign countries (N=58 [20.6%]), as their birthplaces. Of the 265 patients who provided such information, 244 (92.1%) had histories of at least one previous psychiatric hospitalization, and 192 (65.8%) of the 292 patients who provided such information had been homeless for more than 1 year; 98 (33.6%) of the 292 patients said that they had been homeless for more than 5 years.

Of the 297 patients for whom diagnoses were available, 238 (80.1%) were given an *ICD-9* primary diagnosis of schizophrenia, 23 (7.7%) affective disorders; 16 (5.4%) organic brain disorders, and 20 (6.7%) other psychiatric disorders. Two hundred seventeen (73.1%) of the patients suffered from at least one medical condition in addition to a primary psychiatric diagnosis. The most common physical conditions, suffered by at least 20% of the patients, included peripheral vascular disorders, anemias, infestations, and diseases of the respiratory system, particularly tuberculosis. In addition, 103 (34.7%) of the patients had a secondary diagnosis of substance abuse.

The 298 individual patients accounted for 340 emergency room visits at Bellevue Hospital. This is because 37 patients were evaluated more than once in the emergency room, and some of them were rehospitalized during the 1-year study period.

In 286 (84.1%) of the 340 cases, the patients were transported to the hospital involuntarily; 328 (96.5%) resulted in hospitalization (315 [96.0%] of these were involuntary). A number of hospitalizations, medical treatments, and transfers to state psychiatric centers for extended care were challenged subsequently by the patients in 131 court hearings. In the majority of these hearings (N=114 [87.0%]), the court upheld the hospital psychiatrists' recommendations. The patients' average length of stay at Bellevue Hospital was 61.3 days (range=2 to 228 days).

DISCHARGE DISPOSITIONS AND FOLLOW-UP

Discharge dispositions for the 340 visits to Bellevue Hospital were obtained from clinical records. Half of

TABLE 1. Follow-Up Contact Location of 298 Homeless Subjects Involved in a Program to Help the Homeless Mentally Ill

Location	Number	Percent
State psychiatric center	73	24.5
Community residence[a]	62	20.8
Transitional shelter program	9	3.0
Nursing home or health facility	6	2.0
Bellevue inpatient ward	1	0.3
With relatives or alone	12	4.0
On the street[b]	23	7.7
Deceased	2	0.7
Unverified[c]	33	11.1
Unknown	77	25.8

[a] Includes adult homes and supervised single-room occupancy hotels.

[b] The subjects were known to be on the street and were being monitored by Project HELP.

[c] No confirmation was possible by telephone (as of Oct. 31, 1989) that these subjects were still at their last known placements.

the patients were transferred to a state psychiatric center for extended care. This proportion is substantially higher than the 8% rate of transfer to state facilities for the adult psychiatric inpatient population in New York City public hospitals during the same time period (New York City Health and Hospitals Corporation, Office of Mental Hygiene Services, 1988). Other dispositions include discharge to the care of relatives or self (N=65 [19.1%]), to community residences with different levels of support (N=58 [17.1%]), to the transitional shelter program (N=21 [6.2%]), and to nursing homes and other health care facilities (N=13 [3.8%]). In 12 (3.5%) of the cases, patients left the hospital without consent.

Follow-up information was obtained by means of telephone calls made to patients or their aftercare placement agencies at 3-month intervals. The last follow-up calls were made during October 1989, 2 years after initiation of the program. The locations of the patients at this time are presented in table 1. Sixty-three percent of the 298 patients were contacted in person or their location was confirmed through their aftercare setting. At the time of the follow-up contact, 80 patients were hospitalized in either a psychiatric facility or a health-related facility. Eighty-three patients were living in the community in settings such as residences, adult homes, single-room occupancy hotels, the transitional shelter program, with relatives, or by themselves. Two patients were known to be dead, and 100 patients were either back on the streets or their location was unknown. Most of the 33 remaining patients with unverified locations were living out of New York State.

COMMENTS

We can draw only tentative conclusions from these data regarding the benefits patients derived from the interventions of New York City's program. There are several reasons for this. First, the clinical as well as the historical data available for these patients were retrieved from records and were limited in scope. Second, the follow-up contacts with patients or their aftercare agencies were brief and did not include any formal evaluative component. Third, there was no comparison group. Finally, the long-term effects of this program would undoubtedly be affected by the fact that this was a model program that received inordinate public attention and enjoyed an extraordinary investment of enthusiasm and resources.

We can hypothesize, however, that had the program not been implemented, many of these seriously mentally ill homeless patients would have remained in the streets and perhaps suffered progressive physical and psychiatric deterioration. That about 28% of the patients were living in the community and 27% were receiving institutional care 2 years after the intervention suggests a limited but positive impact of the program on the target population. Although comparison is difficult because of differences in samples and methods, this outcome appears to approximate the results of other recent pilot studies on posthospital aftercare of the homeless mentally ill (40, 41).

Given the known difficulties for the mental health care delivery system in monitoring the seriously and persistently mentally ill, it is noteworthy that some form of contact was made at 3-month intervals with 63% of this group of patients for up to 2 years following their initial inpatient care episode. In this regard, our experience with the program supports the importance of patient tracking systems, case management, and interagency clinical as well as administrative coordination and linkages to enhance continuity of care through continuity of information for this population (42, 43).

Our findings suggest that the provision of needed care to the multiply disabled homeless mentally ill should include aggressive outreach interventions and, if necessary, involuntary hospitalization. Predictably, treatment programs such as New York City's raise the perennial dilemma between protecting disabled individuals and safeguarding their civil liberties, no matter how self-destructive their choices may be. In addition, the cost to the mental health care delivery system is considerable, since due to lengthy legal procedures, time-consuming medical tests and treatments, and the need for intensive psychosocial interventions and discharge planning, the hospital stays of these patients tend to exceed the standard for acute-care hospitalization.

The large proportion of patients transferred to a state psychiatric center for extended care, although perhaps reflective of the program's well-established access to a state facility, probably also suggests that many of these patients represent a subset of severely psychiatrically impaired homeless in need of long-term institutional psychiatric care (44). In this regard, preliminary medical record data suggest that our group of homeless patients may be different from the 628 homeless mentally ill persons evaluated at Bellevue Hospital's emergency room independently of the program during the same time period. Specifically, fewer homeless patients in this latter group carried a diagnosis of schizophrenia (N=316 [50.3%]), more of them were male (517 [82.3%]), and on average they were younger (mean age=34.7, median=33) (New York City Health and Hospitals Corporation, Office of Mental Hygiene Services, 1989).

The New York City program illustrates how mental health professionals can work with policy makers to develop programs that are responsive to this often neglected, multiply disabled population (45–49). Further, apart from its tangible impact on the target population, public reaction to the program, as reflected by the media, suggests that, with the exception of some civil libertarians who expressed concern about the program's potential for abuse of patients' civil liberties, it created a positive impression of the actions taken by the city to address the problem. Although the city program targeted a small subgroup of the homeless population and had a limited impact on the large numbers of homeless mentally ill people living in the streets, there was some public recognition that government officials and mental health professionals cared for these people and were willing to do something about the problem (50–52). In this sense, the program can be judged in terms of its good intentions as well as its tangible results (53).

Although this study is somewhat limited in its generalizability due to the particular characteristics of the New York City patients involved in the program, we believe it has contributed still another piece to the large jigsaw puzzle that is our understanding of the homeless mentally ill (54). Certainly, more research is needed to ascertain the impact of specific treatment interventions on particular subgroups of the homeless mentally ill and to explore what patient and service system indicators may act as predictors of positive or negative outcomes.

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Book Forum

Nancy C. Andreasen, M.D., Ph.D., Editor

GERIATRIC PSYCHIATRY

Histology and Histopathology of the Aging Brain, *edited by Jürg Ulrich. Basel, Karger, 1988, 172 pp., $113.50.*

Alzheimer's disease is probably the central neuropsychiatric issue for our generation of physicians. Psychiatrists are becoming increasingly involved in the care of patients with this disease and in research programs aimed at understanding its etiology. Questions of alterations in neuropsychiatric functions that might occur with "normal" aging are also topics of importance for behavioral researchers and clinicians.

Histopathology of the Aging Brain is a state-of-the-art review of histologic controversies in aging and dementia. The book is relatively short and quite densely written. The editor has brought together focused research summaries from an array of prominent neuroscientists in Europe and Canada. The essays are arranged around major themes in neuroscientific research.

The first section reviews the question of regional brain changes in aging and dementia. Dr. Ball of London, Ont., provides a provocative hypothesis that the hippocampal damage in Alzheimer's disease can account for most of the clinical features of the illness and that neocortical changes are incidental. Current research in alterations of subcortical neuronal projections that occur in Alzheimer's disease is also well reviewed in a chapter by Drs. Berger and Gaspar of Paris. These issues are of great importance for psychiatry because of potential links between disturbances in monoamine metabolism and arousal or affective dimensions of dementia.

The second major section of the book includes two essays that describe recent technical advances in quantitative morphologic analysis of neuronal tissue. Pathologists now have available to them optical-electronic instruments that expedite the quantitative analysis of neuronal and vascular structures.

The third major section of the book presents reviews of current research in cytoskeletal abnormalities found in Alzheimer's disease. The last section of the work reviews some recent immunohistologic work in the neuropathology of Alzheimer's disease, along with more controversial topics such as potential aluminum and viral involvement in the disease.

The virtues of this book are that it is current, thoroughly referenced, and well illustrated. Readers should realize, however, that it is essentially a neuroscientific treatise and will be most useful as a reference book. Clinicians and even some clinical investigators in the area of dementia might not need to purchase such a book. The audience for this work is really those scientists who are engaged in dementia research that requires familiarity with the advancing frontier of histopathologic research in Alzheimer's disease.

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Geriatric Psychiatry and Psychopharmacology: A Clinical Approach, *by Michael A. Jenike, M.D. Chicago, Year Book Medical Publishers, 1989, 381 pp., $54.95.*

There are many books on geriatric psychopharmacology that have been sponsored by various pharmaceutical firms. These texts are fine as introductions to the field but really do not go into the crucial problems with enough depth to be useful for the thoughtful clinician. Jenike's work goes beyond the average work and provides a much more solid reference than anything currently available.

The work is reminiscent of my favorite psychopharmacology text, Baldessarini's *Chemotherapy in Psychiatry* (1). Jenike's work is approximately the same length as Baldessarini's, providing plenty of room for in-depth discussion and references. Another excellent trait common to both books is the generous use of summary tables to highlight key relationships.

Geriatric Psychiatry and Psychopharmacology covers all the major topics relating to geriatric psychiatry from a biological perspective. These include mental status and neuropsychiatric examination of the geriatric patient, metabolic changes with aging that affect drug pharmacokinetics, affective disorders, dementias, psychosis, violence, disruptive behavior, anxiety disorders, sleep disorders, delirium, drug abuse, obsessive-compulsive disorders, neuroimaging, and the interaction of psychosocial factors, psychotherapy, and biological approaches. Thus, the book covers the main areas, and it does so in detail.

Particularly interesting and novel chapters include those on anxiety disorders and obsessive-compulsive disorder. Those of us who have been out of training for more than a few years may not be aware of the explosion of information on these disorders available now in modern psychiatry. These chapters provide much useful information for clinicians who want to get up to speed in these rapidly expanding areas.

All in all, this is a fine work that is particularly timely given that an examination for Added Qualifications in Geriatric Psychiatry is to be part of the American Board of Psychiatry and Neurology examinations.

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1. Baldessarini R: Chemotherapy in Psychiatry: Principles and Practice. Cambridge, Mass, Harvard University Press, 1985

JEROME A. YESAVAGE, M.D.
Palo Alto, Calif.

The Brain in Human Aging, *by Gene D. Cohen, M.D., Ph.D. New York, Springer Publishing Co., 1988, 251 pp., $26.95.*

This work provides a general review of biochemical and other theories of the aging brain. The first section of the work, the Brain and the Aging Process, essentially deals with normal aging. The first chapter, "The Biology of the Normal Aging Brain," is a succinct summary of biology, and "Behavior and the Aging Brain" covers the major behavioral theories. The chapter on behavior is probably the most useful to the psychiatrist reading the work who may not be aware of the major psychological theories that affect geriatric psychiatry. Dr. Cohen does an excellent job of providing careful reviews of the major topic areas and up-to-date references of these areas. The next chapter, "Interrelationships Between the Aging Brain and the Aging Body," would be of interest to the consultation-liaison psychiatrist. Dr. Cohen successfully attempts to clarify the interrelationships of gastrointestinal distress and psychological symptoms in the older patient.

The second major section deals with disorders and diseases in the aging brain. The first major topic is differential diagnosis. Dr. Cohen not only discusses research but also reaches into his rich clinical experience to provide illuminating examples of diagnostic problems. There is a nice review of the theories of Alzheimer's disease and then a more in-depth discussion of the diagnosis and discussion of treatments for patients with the illness. Again, Dr. Cohen provides excellent clinical examples of treatment interventions.

Dr. Cohen finishes the work in a section on capacities of the aging brain. Here he discusses the resiliency and repair of the aging brain, the aging brain in creativity, and theories of aging and life extension. The book concludes with a number of useful appendixes on criteria for the diagnosis of Alzheimer's disease, various tests for dementing disorders, and lists contrasting psychotropic medications.

This book is quite well organized and clearly written so that the novice in the field can pick it up and rapidly get an idea of the major theories of geriatric psychiatry. The book complements the work of Lazarus and Mershon, *Essentials of Geriatric Psychiatry* (1), which provides, in outline form, information that is essential for understanding geriatric psychiatry and probably for passing the Board examinations for Added Qualifications in Geriatric Psychiatry. Dr. Cohen covers much of the same territory in terms of the facts but covers it in a rather lively and clinical manner. Dr. Cohen's book is also more broadly based, and he delves into psychosocial issues that are beyond the core curriculum in geriatric psychiatry.

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1. Lazarus LW, Mershon SR (eds): Essentials of Geriatric Psychiatry: A Guide for Health Professionals. New York, Springer, 1988

JEROME A. YESAVAGE, M.D.
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Etiology of Dementia of Alzheimer's Type, *edited by A.S. Henderson and J.H. Henderson. New York, John Wiley & Sons, 1988, 251 pp., $76.95.*

This is a most unusual book. It is a report of the Dahlem Workshop on Etiology of Dementia of Alzheimer's Type, held in Berlin in December 1987. I am uncertain whether it will appeal to most psychiatric readers, despite its unique format and substantial value. My judgment does not reflect low esteem for this carefully conceived volume (indeed, it is an excellent work); rather, I doubt that it meets the needs of many and expect that it is too complicated for most clinicians, including psychiatrists, neurologists, and neuropsychologists.

That is unfortunate because this model text reflects the collaborative work of scientists struggling to understand the pathogenesis and pathophysiology of the prevalent but elusive Alzheimer's disease. It is a product of a Dahlem Conference, a uniquely collaborative, highly structured format that apparently forces participants to shed parochial views and work together in groups in an attempt to generate ideas and hypotheses for new research. The book is a combination of chapters written by participants before the meeting and reports of work groups at the meeting. The chapters are condensed, fact-filled reviews that together cover the entire waterfront of issues, from fundamental neurobiology to clinical symptoms and psychosocial factors.

The book is divided into four informal sections, each ending with a group report. These terse, question-filled summaries consider broad topics, including risk factors; expression and symptoms; the molecular, biological, and genetic basis of cell injury; and the relationship between normal aging and late-life dementing diseases. No one opinion prevails, and minority views are duly noted.

Technical terms and concepts are explained briefly, but this book is not for the novice. Its emphasis is rightly on the basic neurobiological aspects of disease discovery, although clinical and environmental concerns are given ample attention. I suspect that the best audience for this book is the reader with a defined purpose, such as the clinical researcher who wants a relatively current and broad view of the basic science literature or the basic scientist who wants a brief but complete summary of the major clinical questions yet to be answered. It is also an excellent review for the student who has finished the preliminaries and wants to encounter the sophisticated but demanding product of a group composed of biochemists, epidemiologists, neurobiologists, neurologists, psychologists, and psychiatrists. The book repeatedly emphasizes the number of unanswered questions facing researchers studying dementia of the Alzheimer's type and is particularly strong in illuminating directions for future investigation. I found especially valuable the report on expression and symptoms and the report on cell injury. No doubt, that reflects my own interests, and I am certain that other chapters will prove equally useful.

I know of no similar work in psychiatry. That may reveal my ignorance, but I suspect it also reflects a unique quality that is so heavily emphasized in this work. The scientific process often involves three roughly defined phases of enlightenment—recognition, association, and, finally, discovery. Movement along this continuum may be neither orderly nor premeditated, but, at its best, thoughtful progression is an explicit aim. The search for the etiology of dementia of the Alzheimer's type has passed largely beyond the recognition phase. Investigators can, for the most part, distinguish patients (or brains) with Alzheimer's disease from those afflicted with other disorders. Indeed, we see in this book the attempt to make thoughtful associations, even as recognition is acknowledged to be incomplete. Given recent findings, such as the apparent linkage marker for some familial cases of the disease on chromosome 21, one feels the movement toward fundamental discovery. However, the investigators who participated in this conference make clear that no single discovery will clarify the basis for all cases of this apparently heterogeneous disorder, nor will discovery of etiology guarantee the immediacy of a cure.

Thus, this book reflects the work of investigators who are at a different stage of the scientific process than most of us who spend our time studying primary psychiatric disorders. We still struggle with recognition. As much as we attempt to make associations, often we are undercut by the arbitrariness with which we separate one syndrome from another.

Another lesson is evident for psychopathologists and budding neuropsychiatrists. Frequently we gaze enviously at our colleagues who study diseases that manifest a defined neuropathological substrate. It is clear from this text that the plaques and tangles of dementia of the Alzheimer's type are an elusive gold standard, at best, and this work provides a warning to be cautious when considering neuropathology as the primary validating marker of a CNS disease process. Plaques and tangles, like clinical symptoms, are secondary or tertiary disease phenomena. Although investigators have sought to correlate these pathological hallmarks with clinical symptoms or to relate cell loss to symptoms, each finding is the reflection of a more fundamental abnormality. Similarly, psychopathologists must be wary of viewing apparent neurobiological alterations as a gold standard against which to compare clinical phenomena; they both must be viewed against the backdrop of other ill-defined disruptions, some isolated to the nervous system but others, perhaps, resulting from systemic disorders that are most prominently expressed centrally. Moreover, as emphasized by the authors of this text, there is a gulf between knowing where pathology strikes and understanding how these brain changes lead to alterations of behavior.

This book has many lessons for psychiatric researchers and other students who want to stretch themselves substantially. It is not a useful introductory text or manual for clinicians who wish to learn more about the symptoms and signs of dementia of the Alzheimer's type, or about differential diagnosis and treatment. For some, I cannot recommend it highly enough, but I warn others to avoid it.

(On a somewhat sorrowful note, I would add that it appears the support for the Dahlem Conferences has been diminished or discontinued [1]. If this volume reflects the overall quality of these conferences, discontinuation of such meetings will be a general loss to science.)

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1. Dahlem Conference faces ax. Science 1989; 245:122

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ADDICTION

Assessment of Addictive Behaviors, *edited by Dennis M. Donovan and G. Alan Marlatt. New York, Guilford Press, 1988, 497 pp., $39.50.*

This volume sets out to provide the most current information on the general category of addictive behaviors. The authors note that the intended audience for the book "includes students, clinicians (therapists and counselors), and researchers who are working in the field of addictive behaviors." Each chapter has a short clinical précis, and the book as a whole clearly presents its material in a manner that gives important data to students or researchers in the area of addictions. A great deal of research and empirical data is presented that may be too detailed for the practicing clinician.

The prime focus of the work—that addictive behaviors, irrespective of the addiction, have many similarities—is extremely important. Most professionals in the field have been aware for a long time that many of their patients have been or could be multiply addicted. It is also important, as the editors note, to make accurate assessments of patients and all of their addictive behaviors before launching into treatment.

In accordance with their concept that all of the addictive behaviors can be categorized within a biopsychosocial mold, the editors examine each of the major addictions—alcohol, eating disorders, and other drugs—within this same psychosocial framework. The individual authors present much pertinent and relevant data from their own research in their areas of expertise. Many of the authors also present parts or all of the screening devices that they have developed to assess addicted individuals. The reader is faced with an almost overwhelming array of data in each chapter.

This book is most valuable if it is initially read as an overview of the important concepts and then reread in portions. In this way readers can distill the techniques of assessment that they might want to pursue from either a research or a clinical perspective.

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The Psychopharmacology of Addiction: British Association for Psychopharmacology Monograph 10, *edited by Malcolm Lader, D.Sc., Ph.D., M.D., F.R.C.Psych. New York, Oxford University Press, 1988, 179 pp., $55.00.*

This monograph has a number of particular attractions. First, its editor is an internationally renowned psychopharmacologist based at the Institute of Psychiatry, University of London, one of the leading centers of its kind in the United Kingdom. Second, the contributors, each with outstanding reputations and bodies of work behind them, present a genuinely international outlook. Although most are British, the contributors include representatives from the United States, Canada, and Greece. This worldwide perspective is particularly important in supporting those elements of the volume which address the interplay of the biological organism and the culture in which it resides. Third, in view of the amount of information it contains, the book is nicely compact, and each chapter establishes and develops its points efficiently but fully. The physical features of the volume, including its binding, paper quality, and print style, meet the high standards we have all come to expect from the venerable Oxford University Press.

The book is broad in its scope, ranging from molecular pharmacology (one chapter explores neuronal calcium channel adaptation in physical dependence on alcohol and one explores phosphoinositides and transmembrane signaling in ethanol abuse) to behavioral elements of substance dependence (one chapter deals with drug anticipation and drug tolerance) and social considerations (one chapter focuses on psychopharmacology and social psychology).

Shepard Siegel's chapter on drug anticipation and tolerance will, I believe, be most useful to clinicians working with substance-dependent patients because it explores the social and psychological contributions to the phenomena of tolerance and addiction. This approach is applied to both narcotic and nonnarcotic compounds, thus establishing a breadth of scope consonant with the needs of clinical practice. Although biology and pharmacology are central to the study of addiction, it is readily apparent to experienced students of the field that a purely biological focus is insufficient and that, as Siegel points out, "a complete account of tolerance requires an appreciation of environmental influences." Siegel goes on to note that tolerance to a drug is not the inevitable result of repeated administration of the compound but may depend as well on the environment in which the administration occurs. The role of Pavlovian conditioning in tolerance and withdrawal symptoms is here demonstrated to be substantial and persistent in its effects.

I was gratified that nicotine and caffeine are addressed in this monograph as important addictive agents. David M. Warburton's chapter on nicotine is an excellent review of this ubiquitous drug and examines the experimental evidence for three possible models to explain its powerful addictive properties: the euphoriant model (production of pleasurable feelings), the coping model (reduction of unpleasant feelings), and the functional model (general management of everyday psychological needs). Warburton finds the latter two models to be most strongly supported.

The excellent chapter on caffeine by Roland Griffiths and Philip Woodson elucidates the drug's ability to produce physical dependence and reinforcement in humans and laboratory animals. The authors note that this is the most widely used psychotropic agent in the world and that its consumption patterns are in many ways characteristic of more commonly recognized drugs of abuse. Although they present substantial data to support their assertion that "caffeine has the cardinal features of a prototypic drug of abuse," Griffiths and Woodson do not offer prescriptive advice. Rather, they wisely conclude that "a meaningful classification of caffeine, relative to more widely recognized drugs of abuse, should await resolution of the health risk controversy."

The remainder of the book is devoted to benzodiazepines and opioids, including Lader's lead chapter, one by Siobhan M. Murphy and Peter Tyrer on benzodiazepine tolerance and dependence, a chapter on the in vitro pharmacology of selective opioid ligands, and one on the role of opiate mechanisms in social relationships. Each chapter of the book is compact but complete, well edited, and well supported by scholarship. There are occasional unfortunate lapses into obfuscatory syntax ("It would be a most remarkable coincidence that most smokers restrict their smoking habits to a leaf which is the only one which also contains nicotine"), but clearer writing is more typical of the volume. Perhaps editorial comments between the chapters would help to unify the volume and develop its themes more systematically, but the quality of the editing is generally superior to that seen in multiauthored collections of medical papers. I would have expected the inclusion of important material on phencyclidine and the role of excitatory amino acids in addiction. I fear that the omission of this material and of chapters on cocaine in its multifarious forms, which we know all too well has become an international social and public health scourge, already begins to date this 1988 publication.

Because the chapters can support themselves individually, the absence of unifying comment or even an introductory chapter does not seriously compromise the utility of the book. At first blush it might seem outrageously overpriced, but there is a lot of quality hiding in this small package, and I recommend the book to the many scientists and clinicians who are struggling daily to make some headway in the pandemic of substance addiction.

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CHILD PSYCHIATRY

The Preschool Child: Assessment, Diagnosis, and Treatment, *by Paul V. Trad. New York, John Wiley & Sons, 1989, 658 pp., $69.95.*

The author of this book quite correctly states that it deals with a relatively neglected life period. Much more effort has gone into infant research and into school-age children. His book is divided into five parts that cover essential areas: The Developmental Perspective, Assessment, Clinical Syndromes, Specific Risk Factors During the Preschool Years, and Management. The book is replete with case histories and more than 600 references. It cannot be said to be biologically or dynamically oriented because both are represented and integrated. The author is a psychoanalyst but is obviously well read in neurobiology, genetics, and psychopharmacology.

The differences between *DSM-III* and *DSM-III-R* as well as changes that the author hopes will be made in *DSM-IV* are mentioned frequently. Nosology in children is notoriously difficult because of the constant changes in growing youngsters, and nowhere is this more true than in the preschool child. Reading the book, I was repeatedly struck not only by constant advances in our knowledge but the enormous amount we have yet to study.

Since the volume is so large and the subjects so complex, space permits only a general screening and special attention to particular details.

Part one, The Developmental Perspective, is a useful discussion of the emotional development of the preschooler and infant along with Piaget's concept of intellectual development, particularly the relationship between cognitive growth and aggression. A case history is presented to illustrate the discussion.

Part two, Assessment, covers a broad spectrum ranging from *DSM-III-R* through family psychopathology and physiological testing to neuroendocrine determinants. Here one of the problems of *DSM-III-R* comes to light—its lumping together those conditions first appearing in infancy, childhood, or adolescence. Many syndromes do not usually occur during the preschool years but, rather, in infancy or adolescence. The author points out that "psychiatric nosology in children is in a constant state of flux." Because children move so quickly through time in terms of development and integration of the environment, the task of meticulously and globally assessing each child for possible etiologies is particularly crucial and at the same time very difficult. The family must be thoroughly examined as well as neuroendocrinological correlates of the child's cognitive development, mental status, temperament, neurological status, and the results of appropriate psychological tests. The author's discussion of the neuroendocrine determinants of various syndromes is both fairly complete and quite complex. The limbic system—including the hypothalamic-pituitary-adrenal axis—mediates the individual's interaction with the environment. Within this axis, serotonin, norepinephrine, and dopamine are particularly crucial. Dysregulation of the limbic system—whether genetic, constitutional, environmental, or a mixture—can result in a variety of syndromes. Some studies of the chemistry involved have been done as early as infancy, but most have involved adults. It is here that the old nature-nurture argument is basic but not always clear. Much research remains to be done. Many individuals are predisposed to some type of dysregulation, and minimal external forces can bring on a symptom complex.

Part three, Clinical Syndromes, is made up of 13 chapters on the differential diagnosis of pervasive developmental disorders, learning disabilities, personality disorders, affective disorders, anxiety disorders, attention deficit disorders, sleep disorders, tics, gender identity disorders, somatoform disorders, and suicide.

Part four, Specific Risk Factors During the Preschool Years, comprises two chapters: one on child abuse and neglect and the other on the child's reactions to various kinds of separation, including day care, divorce, and death.

Part five, Management, has three chapters. The first deals with psychodynamic intervention with the preschool child. The second focuses on family therapy, behavioral therapy, cognitive therapy, group therapy, and pharmacotherapy. Finally, there are therapeutic protocols for disorders in the preschool years.

Perhaps the best word to describe this book is "comprehensive." Its thorough review of the international literature often includes presentation of conflicting findings, thus leaving the reader confused. It does, however, point to the areas in need of further research. It takes into account psychoanalytic, biological, and cognitive approaches. Oversimplified, it proposes that each child comes into the world with his or her own endowments and that the environment then begins to take effect. Some children are able to develop successful coping styles, even in the face of a poor environment, but others do not and become ill. Proper assessment of the child and his or her situation allows for better, more accurate evolution and plans for treatment. Multidisciplinary approaches are often called for in both assessment and treatment. The author obviously has available a large pool of consultants and therapists often not accessible to workers in this field.

This book should be useful to any health or mental health worker dealing with preschool children. It would be a valuable addition to the library of any such professionals.

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Handbook of Child Psychiatric Diagnosis, *edited by Cynthia G. Last and Michel Hersen. New York, John Wiley & Sons, 1989, 574 pp., $59.95.*

This book was spawned by the advent of *DSM-III* and subsequently *DSM-III-R*. The editors explicitly state that this book was conceptualized to present research on each diagnostic category for children and adolescents as a "state of the art volume." Without a doubt, the editors succeed in presenting clearly written chapters that provide a valuable reference work for the field of child psychiatry.

The first part of the book focuses on concerns relevant to making a diagnosis, providing a historical perspective on current aspects of nosology, reliability, and validity of disorders. Lewis and Vitulano point out that the field has evolved historically from a singular mode of understanding disorders to a complex interactional model. Trad advocates the importance of evaluating youngsters from multiple perspectives and highlights two basic items for assessment—developmental level and functional or adaptive level. Anthony Costello emphasizes that diagnostic reliability implies that the result of a diagnostic assessment can be replicated. He discusses factors that might affect the degree of reliability. Clarification of diagnostic validity is offered by Routh, who states that "validating diagnostic categories boils down, at least in part, to hypotheses testing about their implications for prognosis, etiology, and treatment" (p. 41).

The second part of the book contains 18 chapters on specific diagnoses; these chapters include empirical research data. They all follow the same format—sections on definition, historical background, clinical picture, associated features, course and prognosis, impairment, complications, epidemiology, familial pattern, differential diagnosis, clinical management, and research findings—which helps the reader compare diagnostic entities.

The format of these chapters resembles that of *DSM-III-R*, and the chapters amplify the statements in *DSM-III-R* by presenting research used to substantiate diagnostic classifications. These chapters are excellent summaries of research findings in child psychiatric diagnosis. Each is written by experienced researchers: Baumeister and Baumeister on mental retardation, Dulcan on attention deficit disorders, Kazdin on conduct and oppositional disorders, Wolff on schizoid disorders, Ornitz on autism, Wolff on obsessive-compulsive disorder, Cantor on schizophrenia, Strober, Hanna, and McCracken on bipolar disorders, Ryan on major depression, Keller and Sessa on dysthymic and cyclothymic disorders, Regan and Regan on somatoform disorders, Fialhov on substance use disorders, Zucker on gender identity disorders, Goldbloom and Garfinkel on anorexia nervosa and bulimia nervosa, Doleys on functional enuresis and europresis, and Kolko on fire setting and pyromania. Each chapter is easy to read, and the complex issues are presented concisely and with relevant references. Therefore, they are an excellent reference compendium that summarizes diagnostic entities in children and adolescents.

The third section of the book focuses on special topics pertaining to developmental issues, diagnostic interviews, epidemiology, and assessment of diagnoses and behavior. The final section focuses on future directions in child psychiatric diagnosis. An intriguing concept presented is that of developmental psychopathology, which emphasizes that "there is no compelling evidence that dysfunction at one point in childhood *definitely* predicts pathology later in childhood. Stability of pathology in childhood seems to be the exception rather than the rule" (pp. 463–464). Methods of documenting the continuities and discontinuities of development are described in this part of the text. The final chapter offers important axioms to consider with regard to psychiatric diagnosis. In this last chapter, Judith Rapoport states, "Diagnosis is a process that will not and should not ever get into a 'true' system, and so we must avoid taking arbitrary stands on questions such as dimensionality versus categorical measurement on particular subcategories. Multivariate factors will always be with us, and major new etiological discoveries will not make them less useful" (p. 531). This text is a fine sourcebook for considerations needed to identify salient issues in conceptualizing *DSM-IV*.

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Beginning Child Psychiatry, *by Paul L. Adams, M.D., and Ivan Fras, M.D. New York, Brunner/Mazel, 1988, 595 pp., $50.00.*

This book is directed toward professionals, especially child psychiatry fellows, who are beginning careers focused on promoting the mental health of children and adolescents.

The book provides a comprehensive overview of child psychiatry and is organized into a number of sections.

The section on disorders of childhood is an excellent introduction to diagnosis as well as an excellent overview of treatment in child and adolescent psychiatry. The careful description of the elements of a comprehensive evaluation would be very useful to those seeking an introduction to this important area of child psychiatry. I would have liked more of an emphasis on the mental status examination, even though its application to the psychiatric assessment of children has not been adequately developed. Its use can serve to standardize this portion of the assessment and help physicians beginning their training not to overlook aspects of mental functioning. Also, the use of a standardized mental status examination allows for better communication of clinical information between professionals. An emphasis on the mental status examination would also be consistent with the very helpful focus in this book on the importance of careful observations of the behavior and nonverbal communications of the child or adolescent who is being assessed.

The clinical examples that fill this text are rich in their descriptions of children and families suffering from psychiatric illness. The clinical examples also contain useful models of an empathic and sensitive approach to the understanding of psychiatrically ill children and adolescents. However, the treatment section, which briefly reviews different treatments, seems to be overly cursory in discussing the operant behavioral therapy techniques that have a widespread application in child psychiatry.

The section on organicity, although it covers important topics, also suffers from a tendency to recommend organic workups that can become fishing expeditions with the physician having no idea what to do with the fish that may be caught (to strain a metaphor to the breaking point). In other words, it is not useful to go fishing diagnostically unless you are prepared to make use of the information. Many diagnostic procedures are relevant only if their findings are consistent with the clinical assessment, and often the diagnostic report indicates that the findings warrant additional studies only if clinically indicated. An emphasis on ordering diagnostic procedures to identify specific CNS etiologies and rule out differential diagnoses would be preferable to the idea of an "organic workup." It will become increasingly important for physicians entering child psychiatry training to be familiar with diagnostic procedures that will help to identify specific neuropsychiatric disorders.

The section on distortions of parenting offers the reader valuable information, as does the section on the child's family. The authors sensitively advocate for the rights of children in families and for the importance of empathic parenting.

The section on personality disorders, although rich in clinical material, advocates earlier (in late latency or early adolescence) diagnosis of personality disorders than I think is routinely possible to do with any validity. Such diagnosis is certainly not possible for physicians beginning their training in child psychiatry. It is important to identify behavior patterns, coping mechanisms, and/or so-called personality traits, but personality diagnoses before later adolescence seem premature.

The section on pervasive developmental disorders lacks a clear clinical example of a "high-functioning" autistic child (1), is insufficiently cautious about the risk of developing movement disorders with the use of neuroleptics, and focuses on the brain stem as the likely location for the neuropathology in autism without describing the other theories, some of which are more plausible (2).

The authors caution against the overuse of medications but seem overly pessimistic about the role of medication beyond the use of stimulants in attention deficit hyperactivity disorder. Anxiolytics are probably underprescribed in children, as are antidepressants. The idea that no condition requires medication or cannot be treated without medication goes too far and is not consistent with more recent pharmacological research (3). The authors are especially discouraging about the use of anticonvulsant medication, although recent experience would seem to indicate that high-dose monotherapy with certain anticonvulsants is effective for mood instability and, of course, for seizure disorders (4).

The authors also seem to discourage hospitalization of children and adolescents, even though there are clear indications for using hospitalization, such as for the child's safety, to allow diagnoses to be established, to initiate treatment with patients who require structure and/or daily assessment to determine treatment efficacy, and to remove patients temporarily from pathological situations (5). Some psychiatrically ill children and adolescents are still best treated with longer-term hospitalization in order to restructure their coping mechanisms and improve their capacity for healthy interpersonal relationships (5).

To summarize, Drs. Adams and Fras have written a comprehensive textbook that introduces physicians and other professionals entering the field of child psychiatry to diagnosis, treatment, and understanding of the child in his or her family. The authors share their years of clinical experience and wisdom throughout the book. This comes through most clearly in the rich clinical examples that are used in the sections of the book focusing on disorders of childhood. This book is well worth the time of anyone who would like to view child psychiatry and advocacy for children through the eyes of two gifted clinicians.

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Assessment of Personality and Behavior Problems: Infancy Through Adolescence, *by Roy P. Martin, Ph.D. New York, Guilford Press, 1988, 399 pp., $35.00.*

The title of this book is challenging and provocative. This volume discusses an important issue that has its derivation in early phases of human development. The title suggests that a new area of emotional development will be discussed—the issue of personality assessment. By placing the word "personality" before "behavior problems" in the title of this book, the author entices a reader to wonder whether there are specific implications to this. However, this book is not a theoretical text that espouses substantially new ideas about personality development. Rather, it is essentially about assessment and, as a result, is well suited to graduate psychology students and others involved in research in personality in children and adolescents.

The author states that this book is "devoted almost exclusively to the quantitative description of persons" (p. 14). It covers a very complex theme of human psychology that has not been clearly defined and requires continued research. The book has an enthusiastic tone and attempts to integrate past research work with an emphasis on the need to continue developing new approaches. The author emphasizes that "those with an interest in assessment of social and emotional behaviors in children have much to look forward to in the next few decades; a new empirical foundation for study of both specific behaviors and personality appears to be on the horizon" (p. 19).

The book attempts to provide an empirical orientation to understanding personality assessment in children. It intends to cover "generalized behavioral tendencies" that involve traits or personality constructs. A basic premise is to avoid theory-based practice and to highlight "vigorous empirical and psychometric criteria" founded on a behavioral orientation. For example, assessment instruments that have been empirically evaluated with regard to reliability and validity are discussed, and techniques are less emphasized.

The book is divided into four main parts. Part one describes concepts of personality theory and assessment, including temperament, personality structure, traits, and behaviors and whether personality is consistent over time. Another concern is whether personality variables are useful in predicting other types of behavior. However, the literature reviewed in this part of the book is primarily about adults, and special issues for children and adolescents are not extensively highlighted. The author recognizes that the concept of personality is confusing and used in different ways. In this book, he says, "personality assessment refers to the assessment of relatively stable characteristics in the social-emotional realm . . . that is, nothing is implied in the use of the word personality other than a generalized characteristic that has some situational and temporal stability" (p. 7). The book attempts to discuss personality assessment within the context of a very broad framework.

The second part of the book is devoted to "basic aspects of instrument and assessment design" (p. 41). It is a general overview of theoretical and practical issues in measurement and test construction. Examples are given for specific tests.

Parts three and four focus on the main issues of personality assessment of youth. The author describes a number of standard tests, rating scales, and self-report instruments for infants, toddlers, preschoolers, elementary school children, and adolescents. Specific tests are described with respect to normative data and reliability and validity. In this respect, the book is a good reference on research instruments. These sections include clinical examples and an appendix that lists recently published articles using these instruments.

In summary, Dr. Martin is correct in stating that this book is for students because it is a basic text offering a good review of the concepts relevant to an empirical type of personality assessment of children and adolescents.

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How Old Is Old Enough? The Ages of Rights and Responsibilities. Report 126, *by the Group for the Advancement of Psychiatry Committee on Child Psychiatry. New York, Brunner/Mazel, 1989, 117 pp., $17.95.*

Traditionally, committee reports from the Group for the Advancement of Psychiatry have been on the cutting edge of psychiatry. This volume does not break with tradition. The Committee on Child Psychiatry has developed a monograph that discusses in depth the differences among chronological, emotional, and developmental ages. The volume pleads that society, particularly the courts and the judicial system, should evaluate each child in regard to his or her developmental age rather than chronological age. In a series of chapters that follow logically, the authors first look at age with a historical perspective. Then they discuss emotional and cognitive development from a variety of theoretical points of view. In chapter three, they briefly survey how the law has looked at chronological age in regard to property rights of children, drinking and driving, religious issues, and sexual and family issues. In chapters four and six, the authors examine two specialized areas that are quasilegal in nature—competency to consent or dissent as a subject in research and competency as a witness in court. One other chapter deals with the authors' opinions in regard to children's rights, not as they are articulated by law or codified in law but, rather, those basic human rights all children should be afforded, such as the right for privacy, the need for respect, the need to play and be childish, and the need to gain autonomy and personal control.

The reader who expects a legal treatise or a law review article summarizing the legal rights of children in the United States today will be sadly disappointed. However, readers who expect a general overview of some of the areas where child psychiatry as a discipline can make a contribution to the legal rights and responsibilities of children will be much more satisfied. This volume is timely in that the Supreme Court recently faced critical decisions regarding the very issues that the volume discusses. In 1988 and 1989, the court considered cases where the chronological age of a child affected decisions regarding the death penalty. The questions asked included, Is the death penalty for a 16- or 17-year-old adolescent cruel and unusual punishment? What is the current consensus of society (not child psychiatrists) in regard to the death penalty for 17-year-olds? and What should society consider in regard to the execution of the mentally retarded? Unfortunately, in their deliberations, the court did not seem to take into account information provided by social scientists. The court is now facing similar questions in regard to the issues of an adolescent's ability to consent to an abortion competently with or without parental permission. I must say that this book provides no guidelines in regard to specific issues such as execution and abortion, but it is a nice overview of many areas where the knowledge and ability of child psychiatrists to discuss the physical, emotional, cognitive, and social aspects of both normal and disordered development contribute to the thinking of our colleagues in the law.

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Reprints of Book Forum reviews are not available.

Letters to the Editor

Antidepressant-Induced Mania

Sɪʀ: The following case of drug-induced mania posed a diagnostic dilemma.

> Ms. A, a 31-year-old married mother of three, with no personal or family history of major depression or bipolar disorder, intermittently came for treatment of her dysthymia and dependent personality. Since adolescence she had experienced chronic dissatisfaction with herself and frequent crying spells, but she had never had problems with sleeping and eating or thoughts of suicide.
>
> Fluoxetine, 20 mg/day, was started, and Ms. A improved after 2 weeks, as manifested by an increased energy level, improved self-esteem, and cessation of the crying. After another 2 weeks, however, she was brought to our hospital in handcuffs. She had slept and eaten very little, had spent excessive money at garage sales, was expansive in mood and irritable, and had impaired judgment. She had broken into a nearby house, accused her minister of murder, and physically attacked three policemen.
>
> Ms. A's manic psychosis resolved after the fluoxetine was discontinued. Low-dose thioridazine was given, and she was discharged after several weeks.

What diagnosis should this patient have been given? Organic mood syndrome connotes a temporary condition, a favorable prognosis, and a medication-free observation period, while bipolar disorder connotes a chronic illness, a graver prognosis, and likely long-term administration of lithium.

DSM-III-R states that the mania of organic mood syndrome is usually caused by toxic or metabolic factors, including hyperthyroidism and use of psychoactive substances such as amphetamines and steroids. The mania of bipolar disorder arises spontaneously or may be precipitated by psychosocial stressors, childbirth, or antidepressant somatic treatment (drugs or ECT). This last should *not* be considered an "etiologic organic factor" (*DSM-III-R*, p. 217). In drug-induced mania, "a history of previous Mood Disorder in the person or in family members suggests that the substance merely triggered a Mood Disorder in a person who was particularly vulnerable to the organic factor" (*DSM-III-R*, p. 112).

Why are amphetamines—substances that are used to treat depression (1, 2)—listed as etiologic organic factors while "somatic antidepressant treatment (e.g., drugs, ECT)" is not? Insofar as differing psychoactive substances may trigger mania, the crucial factor is the state of the affected patient rather than the triggering agent.

Although our patient had a mood disorder (dysthymia), her lack of a family history and a prior personal history of mania leads us to choose the more benign diagnosis of organic mood syndrome. During an 8-month medication-free follow-up, the patient's dysthymia remained, but she has showed no symptoms of mania.

The writers of *DSM-IV* should reexamine the concept of an "etiologic organic factor." Also, we suggest that prophylactic antimanic medication may not be necessary for patients such as ours who experience a first manic episode while taking fluoxetine or other antidepressant medications.

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Transient SIADH Associated With Fluoxetine

Sɪʀ: Hyponatremia has been recognized as an uncommon side effect of fluoxetine. In some cases, fluoxetine may have been associated with the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) (1, *Physicians' Desk Reference*, and personal communication from Dista Products Co.). We wish to report a case of documented SIADH in a patient treated with fluoxetine alone, which resolved after discontinuation of the drug and did not recur with its readministration.

> Mr. A, a 59-year-old white man, was hospitalized with a several-month history of depressed mood, 25-lb weight loss, initial and terminal insomnia, anhedonia, decreased concentration, fatigue, and passive thoughts of death. He had no significant medical history. An organic workup included normal findings on thyroid function tests, head CT scan, and EEG. Routine chemistries revealed only mild glucose intolerance. His depressive symptoms responded well to nortriptyline, but he developed obsessive thoughts and compulsive behaviors without increased water drinking. The nortriptyline was gradually discontinued, and fluoxetine was started in order to treat concurrently the depression and the obsessive-compulsive disorder, which had been confirmed by additional history-taking. Both conditions improved, and the patient was discharged on a regimen of 60 mg/day of fluoxetine.
>
> Mr. A discontinued the medication and was readmitted to the hospital 10 days later with worsening symptoms. Fluoxetine was reinstituted, and the dose was increased to 80 mg/day. On readmission, the patient's serum sodium level was 137 mmol/liter. Three weeks later it was 125 mmol/liter, with a measured serum osmolality of 269 mOsm/liter, a urine sodium level of 45 mmol/liter, and a urine osmolality of 509 mOsm/liter. Mr. A was euvolemic and had normal BUN and serum creatinine levels. Results

of repeat thyroid function studies were also normal. His morning free cortisol level was slightly elevated, consistent with the diagnosis of depression. At that time his serum vasopressin level was inappropriately normal (8.6 pg/ml; normal range=1.0–13.3 pg/ml) given his hyponatremia and hypo-osmolality. A combined insulin tolerance/gonadotropin-releasing hormone/thyrotropin-releasing hormone test found no significant endocrinological abnormalities. An evaluation for occult malignancy revealed only benign colonic polyposis. Fluoxetine, the patient's only medication, was discontinued. Within 3 days his serum sodium level and osmolality returned to normal. One week later, he was rechallenged with fluoxetine, 80 mg/day, a dose that he has tolerated for 3 months to date without recurrence of hyponatremia.

The diagnosis of SIADH secondary to fluoxetine was based on the serum and urine electrolyte abnormalities, normal volume status, normal endocrinological function, and absence of malignancy and other medications. In other cases, this diagnosis was complicated by dehydration, additional medications (*Physicians' Desk Reference* and personal communication from Dista Products Co.), or the failure to assess thyroid and adrenal function (1). The SIADH resolved in 3 days, which is approximately equal to the half-life of fluoxetine but shorter than that of its primary metabolite (2). Fluoxetine has been associated with a number of endocrinological changes in animals, including increased vasopressin levels in the portal pituitary circulation in rats (2). This case confirms fluoxetine as a cause of SIADH that may be rapidly reversible and may not contraindicate subsequent use of the drug.

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Additional Cases of Suicidal Ideation Associated With Fluoxetine

SIR: I read with interest the article by Martin H. Teicher, M.D., Ph.D., and associates entitled "Emergence of Intense Suicidal Preoccupation During Fluoxetine Treatment" (1) and would like to report a similar case.

Ms. A, a 38-year-old married white woman, was admitted to an affective disorders inpatient unit for evaluation of a recent episode of depressive symptoms and suicidal ideation. She had always felt fatigued and depressed in winter but had never received psychiatric evaluation or treatment. Following two ectopic pregnancies 8 years earlier, she had developed constant knife-like pelvic pain, abdominal bloating, increased carbohydrate consumption, joint pain, and mastalgia. Oral progesterone, 400–1000 mg/day, partially alleviated these symptoms. Eight months before admission, the patient underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy. The pelvic pain and associated symptoms subsided postoperatively but then recurred.

Believing that her pain was partially psychogenic, Ms. A's gynecologist referred her to a psychiatrist, who prescribed imipramine, 10 mg/day. Because of headaches and blurred vision, imipramine was discontinued and fluoxetine, 20 mg/day, was started. Ms. A experienced initial improvement of the pelvic pain, but approximately 4 weeks after starting fluoxetine, she developed intense suicidal preoccupation and severe depression. She also experienced hypersomnia, poor concentration, anorexia, and a feeling of being "stoned." In addition, she experienced nightmares, blurred vision, lightheadedness, and a visual hallucination in which she saw her deceased mother. Whenever she saw a razor, she became intensely preoccupied with killing herself. She attempted suicide by carbon monoxide asphyxiation and was admitted to a local hospital. Fluoxetine was discontinued, and over the next 2–3 days, Ms. A's depression, suicidal ideation, and accompanying symptoms markedly decreased. On admission to our hospital 4 days after discontinuation of fluoxetine, she was completely free of these symptoms.

There are many similarities between Ms. A and the patients described by Dr. Teicher and co-workers. Ms. A developed depression and suicidal ideation approximately 30 days after beginning fluoxetine, had had no previous suicidal ideation or attempts, developed hypersomnia during fluoxetine treatment, and experienced rapid remission of depression and suicidal preoccupation after discontinuation of fluoxetine. In contrast to the previously reported cases, Ms. A experienced initial improvement with fluoxetine before she developed depression and suicidal preoccupation. Whether development of such symptoms while taking fluoxetine is coincidental or drug-related is still not known. It is important that clinicians report similar cases.

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SIR: A recent article in the *Journal* described six depressed patients with atypical features of hypersomnolence and hyperphagia who experienced severe suicidal preoccupation during fluoxetine treatment. We wish to report a similar patient who twice developed intense suicidal ideation in association with fluoxetine.

Mr. A, a 26-year-old man, had had no chronic medical problems and good premorbid functioning, including 3 years of college, an honorable military discharge, and steady work. He had been given a diagnosis of atypical depression, including hypersomnia, carbohydrate craving, psychomotor retardation, and depressed mood. He denied ever having had suicidal ideation. The depression was also accompanied by panic attacks, and the patient was placed on a regimen of fluoxetine, 20 mg each morning, and clonazepam, 0.5 mg t.i.d. Mr. A reported symptom resolution in 4 weeks. After 6 weeks of therapy, however, he began abusing alcohol and feeling suicidal, both for the first time. After 8 weeks the patient discontinued fluoxetine. He had no family history of alcohol dependence, depression, suicide, or other psychiatric disorder.

Mr. A came to our facility with alcohol dependence, benzodiazepine misuse, and depressed mood. He was not taking fluoxetine and denied having suicidal ideation during the preceding month. Liver function test values were mildly elevated; CBC, thyroid, and renal function were normal. A urine drug screen was positive for benzodiazepines. Ten days after discontinuing chlordiazepoxide withdrawal, the patient had daily panic attacks consisting of 10- to 15-minute episodes of a pulse rate over 130 bpm, blood pressure up to 180/112 mm Hg, hyperventilation, diaphoresis, and a fearful state. His depressive symptoms included daily crying spells, psychomotor retardation, anhedonia, 10–12 hours of sleep per night, extreme hunger, and depressed mood. Fluoxetine, 20 mg each morning, and clonazepam, 0.5 mg, were restarted, and there was symptom resolution within 3 weeks. The patient was discharged with disulfuram added to his regimen.

After 30 days of taking fluoxetine, Mr. A was readmitted to the hospital with severe suicidal ideation. In the week before admission he had held a loaded shotgun in his mouth and later planned to crash his car into a bridge. Depressive symptoms had worsened over the previous 2 weeks, with psychomotor retardation so severe that a urinal was kept at the bedside, work was missed, and appointments were canceled. He arose for meals because of carbohydrate craving. He complained of poor concentration, decreased libido, and anhedonia. Fluoxetine, clonazepam, and disulfuram were used as prescribed, and Mr. A denied abusing other medications. There were no signs of alcohol withdrawal, and liver function test values had normalized.

Mr. A was placed on suicide precautions, and the dose of fluoxetine was increased to 40 mg each morning. On the following day he was found attempting to hang himself with his pajama top. Fluoxetine was discontinued and he continued to have fleeting suicidal ideation for 5 days, during which ECT was begun, with excellent response after 10 treatments. The patient then wished to be treated with imipramine, and with that medication he appears to be doing well.

Similar to the six patients described by Teicher et al., our patient had symptoms of atypical depression. He also briefly responded to fluoxetine but then relapsed, with development of suicidal ideation for the first time. After stopping fluoxetine he was admitted for alcohol dependence, underwent withdrawal with chlordiazepoxide, and again started to take fluoxetine because of persistent depressive symptoms. The patient returned to the hospital intensely suicidal. Although this was possibly coincidental, the case is consistent with the proposal that in "atypically depressed" patients, fluoxetine may increase the risk of attempted suicide.

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Discussion of Fluoxetine and Suicidal Tendencies

SIR: The conclusion of Martin H. Teicher, M.D., Ph.D., and associates (1) that intense suicidal preoccupation emerges with "an estimated incidence of 1.3%–7.5%" is simply not supported by their case presentations.

Over the past 2 years, I have treated 100 patients with fluoxetine. About half of this group were Cambodian immigrants who frequently had dual diagnoses of posttraumatic stress disorder and major depression. These patients had done poorly with imipramine because of side effects or with alprazolam because of addiction fears. Their response to fluoxetine was dramatically positive. My Cambodian patients reported that it helped them focus their thinking, did not feel sedating or addictive, and helped them come to terms with their extended holocaust experience. Not one of these Cambodian patients, who had been exposed to years of extreme violence against themselves and their loved ones, displayed a reaction like that mentioned in Dr. Teicher and associates' article.

My American outpatients, a heterogeneous group, were equally enthusiastic about fluoxetine's lack of side effects, along with the improved modulation of emotions. Many of my Cambodian and American patients had intrusive, obsessive, violent thoughts before taking fluoxetine that were greatly alleviated by subsequent fluoxetine treatment, rather than vice versa.

Dr. Teicher and colleagues routinely used doses of 80 mg/day. Two patients had their fluoxetine continued or the dosage increased after a rash appeared—a clear contraindication to continued use of fluoxetine. In one case, a steroid was added to ameliorate the rash while the probable offending agent was still being given. I have found doses of 20 mg every day or every other day to be effective, while higher doses have led only to increased side effects. The hypersomnia, akathisia, and fatique noted in the authors' patients would have led me to decrease the dose, not increase it. Finally, adding a stimulant, as was done in two cases, compounds an iatrogenic problem.

The patients in the study by Dr. Teicher and associates were unique. Clearly, no generalization can be made to other psychiatric populations. These hospitalized, severely ill patients had taken many previous medications. All but one had had previous suicidal thinking, gestures, or attempts. In four of six cases, the patient was taking at least one other psychoactive medication concurrently with the fluoxetine. No statement can reasonably be made about fluoxetine when a patient is simultaneously taking seven other psychoactive medications. Finally, were any of these patients hospitalized concurrently, and might a "contagion" of suicidal ideation have developed among either the patients or the mental health observers?

Patients commit suicide every year with overdoses of traditional antidepressants. It is nearly impossible to commit suicide with a fluoxetine overdose. None of the six patients in this study did commit suicide. A study of any change in the rate of suicide by antidepressant drug overdose since the introduction of fluoxetine might be illuminating.

Fluoxetine is a revolutionary antidepressant with many effective uses. Its relative lack of side effects is impressive. Psychiatric patients could be denied an efficacious, unique medication if the conclusions of Dr. Teicher et al.'s article were accepted uncritically.

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SIR: I would like to take issue with Dr. Teicher and colleagues' inference of an association between fluoxetine and the emergence of suicidal states. All of their cases were very complex treatment failures. Four of their six patients received doses in excess of 40 mg/day, and only one received the dose recommended by the manufacturer, 20 mg/day. However, most striking, and totally ignored in the discussion, was the fact that all of their patients had taken monoamine oxidase inhibitors (MAOIs) previously.

In my own practice, where we have treated over 300 patients with fluoxetine with startling success, we have not observed this kind of suicidal agitation. However, we have consistently found that patients previously treated with MAOIs, even with washout periods of 2 months or more, experienced a high sensitivity to the arousing effects of the drug and frequently reported a dysphoric kind of agitation and jitteriness. One wonders if MAOIs leave behind an enduring neurophysiological alteration that creates this particular kind of serotonergic hypersensitivity.

It would be catastrophic if Dr. Teicher and associates' article gave rise to hysteria that prevented patients from having the benefit of this unique and effective drug.

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Dr. Teicher and Associates Reply

SIR: Dr. Miller's letter is interesting and important and provides additional support for the use of low doses of fluoxetine—for some patients, possibly even lower than the recommended daily starting dose of 20 mg. His hypothesis regarding a possible contagion of suicide is interesting but unsupported. Only one of the six patients whose cases we reported was hospitalized during the course of fluoxetine treatment. The remainder were outpatients, and as far as we could tell, having worked with them for several years, they were all completely unaware of one another. Moreover, the reactions we reported occurred over a time span of more than a year.

Although Dr. Miller has not observed a single case of emergent suicidal preoccupation with fluoxetine despite extensive clinical experience with this agent, his observations do not diminish the reality of this problem. Two of our patients experienced this adverse response while taking relatively low daily doses (20–40 mg) of fluoxetine, and two patients developed this response while receiving only fluoxetine. Furthermore, Fava and Rosenbaum (1) recently presented data on the emergence of suicidal ideation from a series of about 1,017 patients treated by 27 different psychiatrists. They reported a 3.5% incidence of suicidal ideation emerging de novo in patients receiving fluoxetine only and a 6.5% incidence in patients receiving a combination of fluoxetine and a tricyclic antidepressant. In June of this year, Dr. Barbara Geller, of the University of South Carolina, stated at an NIMH-sponsored workshop on the psychopharmacology of adolescent depression that she had to abruptly terminate an open-label study of fluoxetine in adolescent outpatients with serious endogenous depression because of the de novo emergence of intense violent suicidal and/or homicidal ideation in five patients. Thus, we believe that this is a real adverse effect that occurs in certain patient populations under as yet unspecified treatment conditions. Dr. Miller's letter is important in identifying patient populations and treatment strategies that may minimize the likelihood of this response. We hope that continued reports of both positive and negative experiences will more clearly identify patients who may be at risk and will delineate means of using this agent most safely.

Regarding Dr. Berkley's letter, we take issue with two of his statements. First, he states that only one patient received the dose recommended by the manufacturer, 20 mg/day. According to the package insert and company literature, this is the recommended starting dose, and the dose may be increased to a maximum of 80 mg/day after several weeks if no clinical improvement is observed with a lower dose. This recommendation was followed for five of the six patients reported. Those who went on to receive high doses did so gradually (patient 3 had an increase to 80 mg/day over 5 weeks, patient 5 had an increase to 80 mg/day over 8 weeks, and patient 4's dose was increased to 80 mg/day over 12 weeks). The only exception was patient 1, who took part in a clinical trial of fluoxetine designed to determine dosing parameters prior to approval by the Food and Drug Administration.

Second, Dr. Berkley states that we ignored in our discussion the observation that all of these patients had previously received treatment with MAOIs. On the contrary, we were very aware of the possible sensitizing effects of previous treatments and emphasized this three times in the Discussion section (paragraphs 2, 5, and 9). We also specifically discussed this observation with the manufacturer and strongly urged them to review their records to ascertain whether patients with histories of previous MAOI treatment had a greater incidence of adverse reactions. We should emphasize that only three of our reported patients had had recent exposure to MAOIs. The other three patients had last received MAOI therapy years before the initiation of fluoxetine, making a short-term sensitizing effect unlikely.

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Another Case of Self-Cutting After Combat Stress

SIR: In a recent letter, Roger K. Pitman, M.D. (1) reported a case of self-mutilation following combat stress. We wish to report another such case in a patient with posttraumatic stress disorder (PTSD). Other reports have suggested similar traumatic origins for borderline personality disorder (2), multiple personality disorder (3), and PTSD. Self-mutilation that seeks relief of tension rather than social response has been reported in both people and animals in traumatic situations (4). It is well-known in borderline personalities. Greenspan and Samuel (5) reported similar self-cutting in previously healthy rape victims.

Mr. A, a 42-year-old former Marine, reported a history of self-cutting behavior beginning approximately 1 month after returning from Vietnam. He would cut himself superficially on the wrists, forearms, face, and torso in response to severe bifrontal headaches that developed after arguments with others. In these instances Mr. A would experience intrusive combat-related memories. Cutting himself relieved the headaches and tension; the patient reported that if he did not cut himself at this point, he would often hurt someone else. During these episodes he experienced such perceptual disturbances as loss of color vision, time distortion, and hypesthesia. He estimated that he had resorted to self-cutting on approximately 20 occasions. In addition to this behavior, Mr. A also reported symptoms more typically associated with PTSD, such as hypervigilance, nightmares of combat, and social withdrawal.

Mr. A had served in Vietnam for a year. He had experienced a moderate amount of combat and witnessed the deaths of several friends. After these experiences he became more withdrawn, avoiding interactions with others in his unit unless absolutely necessary. He was involved in several incidents in which he tortured or killed Vietnamese nationals, and he reported persistent guilt over this.

After returning from the war, this patient showed behavior in addition to self-laceration that is sometimes associated with the borderline syndrome. He engaged in polysubstance abuse, was involved in multiple street fights, and made several suicide attempts by drug overdose. However, Mr. A's prewar personality had been markedly different from this. According to his wife, he had been an outgoing person with no history of substance abuse, violence, or criminal activity before his enlistment in the military. He had worked from the age of 7 through his high school years transporting groceries for neighborhood women. Although he reported having been raised by a strict and sometimes harsh father, he denied having been abused in any way during childhood.

We conclude that combat stress can lead not only to the symptoms commonly associated with PTSD but also to self-mutilation for relief of tension. We recommend further investigation into the occurrence of posttraumatic "borderline" behavior.

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Obsession or Worry?

SIR: Diagnostic precision is critical for studying etiology, natural history, and response to treatment. Especially important are clear boundaries between specific diagnostic entities. The boundaries in *DSM-III-R* between obsessive-compulsive disorder and generalized anxiety disorder are blurred. With the exception of worries about contamination, which are specifically assigned to the criteria for obsessive-compulsive disorder, obsessions characteristic of that disorder and worries essential to generalized anxiety disorder are not described in mutually exclusive terms. The manual does not discuss generalized anxiety disorder in the text on differential diagnosis of obsessive-compulsive disorder, and vice versa.

Whether a specific mental phenomenon is considered an obsession or an excessive worry is determined largely by the approach taken by the examiner in exploring the symptom. While obsessions are defined in terms of their intrusiveness, distressing quality, origin within the self, unreasonableness, and the patient's resistance, "excessive anxiety and worry" is assigned no specific characteristics. *DSM-III-R* offers "worry about possible misfortune to one's child (who is in no danger)" as an example of thought content in generalized anxiety disorder. The manual does not discuss whether a person with generalized anxiety disorder experiences such a worry as recurrent, intrusive, distressing, and as originating in the self, although worries would seem to have these attributes if the person is symptomatic. The question of whether such a worry is recognized by the sufferer as unreasonable is not discussed in *DSM-III-R*, and so its use as a distinguishing characteristic is not addressed. One might argue that an obsession has some irrational core, represents an unnatural interruption in continuity of thought, or is resisted, whereas a worry seems more plausible, is more consistent with the overall progression of thought (i.e., persistent worry about everything), and is little resisted. The diagnostic criteria and the text of *DSM-III-R* do not discuss these potential points of distinction. The presence of compulsions cannot be the arbiter in all cases, since compulsions are not always present in obsessive-compulsive disorder. Further, generalized anxiety disorder is often accompanied by efforts to seek reassurance, such as telephoning and checking the clock—phenomena that might be considered compulsions. The worries of generalized anxiety disorder must be accompanied by symptoms of physiological arousal, but the presence of such symptoms does not preclude obsessive-compulsive disorder, which is often itself accompanied by such arousal. There must be two or more worries to qualify for the diagnosis of generalized anxiety disorder, but obsessions often are multiple.

What is the distinction between a worry and an obsession? Is there one? In our view, *DMS-III-R* does not establish a basis for distinguishing these phenomena or the diagnostic entities they represent. The result is that some cohorts of patients with obsessive-compulsive disorder may include persons with generalized anxiety disorder, and vice versa. This might affect epidemiologic, treatment outcome, and natural history studies. What is the true comorbidity of these two disorders? To what extent are symptoms of one being assigned a role in the diagnosis of both? Perhaps obsessions are like pornography: you know them when you see them. However, for research we must strive to do better.

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Comment on *DSM-III-R* Panic Disorder With Agoraphobia

SIR: As a group of Italian physicians working in forensic psychiatry, we frequently see patients in the correctional field. Having noticed what in our opinion is an imprecision in *DSM-III-R*, we take the liberty of bringing this to *Journal* readers' attention. In *DSM-III-R* under the heading of Panic Disorder, the manual lists only panic disorder with agoraphobia (300.21) and panic disorder without agoraphobia (300.01)

In clinical practice we often see prisoners who have panic attacks with claustrophobia. Recently, we have had three consecutive cases, all of which involve young men in custody who are awaiting trial. In one case the attacks had also occurred before imprisonment; in the other two they appeared only after the men were imprisoned. All three patients are resistant to drug treatment with either tricyclic antidepressants or alprazolam. They have daily to weekly panic attacks, with massive cardiovascular, respiratory, and/or neurovegetative symptoms. Under Italian law such a condition could be grounds for a decision of incompatibility with prison life and concession to house arrest. A judge could therefore consult *DSM-III-R* and fail to find "panic disorder with claustrophobia," although some of the symptoms listed therein (e.g., panic attack when in an elevator) do actually appear to refer to claustrophobia. Of course, these could be classified as panic disorder without agoraphobia. At any rate, the claustrophobic element is specific to the condition in the prison setting, since continuation of imprisonment prevents handling of the case and therefore, according to Italian law, warrants the incompatibility decision.

Would it not be feasible to redesignate the category as "panic disorder with agoraphobia or claustrophobia" and to modify the criteria accordingly? We understand that this problem largely concerns the Italian forensic field. Nevertheless, in view of the worldwide acceptance of *DSM-III-R* as the basic taxonomy in mental illness, *DSM-III-R* should, in our opinion, address the needs of as many national medicolegal systems as possible. Particularly in countries under Roman law, precise legal terminology is of paramount importance.

Incidentally, panic attacks with claustrophobia—mentioned in 1960 by Mayer-Gross et al. (1)—are not mentioned by Uhde and Nemiah (2).

We would be interested to know whether similar cases have come to the attention of American colleagues.

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Seasonal Independence of Decreased Intraocular Pressure Dynamics in Seasonally Depressed Women

SIR: There is evidence to suggest that amplitudes of circadian rhythms are abnormally low in depression (1). We have suggested that also the hemodynamics of the eye may be dampened in seasonal affective disorder. We have found much lower intraocular pressure values during the afternoon hours in seasonally depressed patients than in healthy subjects and a reduction in the rate of secretion of the aqueous fluid in women with seasonal affective disorder before they receive phototherapy.

There are different types of diurnal intraocular pressure curves, the most common one showing a rise during the early morning hours and a fall in the afternoon (2). There is also good evidence of seasonal variations in intraocular pressure, with lower pressures tending to occur in summer (3). In this context, we now wish to report some preliminary data on the seasonal independence of decreased ocular pressure dynamics in a group of women with seasonal depression.

We investigated tonographically seven women aged 25–42 years who had been given diagnoses of a seasonal pattern of major depression according to *DSM-III* criteria. Ten age-matched healthy women served as the control subjects. All subjects gave written informed consent to participate in the study. Studies in both groups were made in summer (the end of May through July) and in winter (December through January). To avoid variations in intraocular pressure that occur during the menstrual cycle, the subjects were examined in the middle of the cycle. To be included, the patients had to have a score of at least 16 on the Hamilton Rating Scale for Depression. Applanation tonometry with a plunger load of 5.5 g was performed at 8:30 a.m. in both seasons. The flow (*F*) of the aqueous humor was counted according to the formula $F=C(P-8)$, in which *C* is the outflow in cubic millimeters per minute per millimeter of mercury, *P* is the applanation pressure before the tonography, and 8 is the episcleral venous pressure.

The results showed that the women with seasonal affective disorder had significantly lower intraocular pressure and flow of the aqueous humor in both seasons. Thus, in summer the mean±SD intraocular pressures of the patients and the control subjects were 13.1 ± 1.4 and 15.8 ± 1.2 mm Hg, respectively, and the F values were 1.5 ± 0.6 and 3.4 ± 0.9 mm^3/minute, respectively ($p<0.01$ for both comparisons). Similar differences were found in the winter months: intraocular pressures were 12.7 ± 1.2 and 16.4 ± 1.5 mm Hg, respectively, and F values were 1.2 ± 0.5 and 2.9 ± 0.7 mm^3/minute, respectively ($p<0.01$ for both comparisons) (Mann-Whitney U test).

Since light has been reported to improve winter depression (4) and to increase the flow of clear fluid in normal eyes (5), we may speculate that the possibility of a decreased flow in seasonal depression might account for an overall decrease in ocular pressure dynamics and thus be responsible, for example, for more erratic diurnal variations in intraocular pressure and less proper responses to such environmental factors as the darkness and cold temperature of winter days. Again, since prolactin is known to stimulate reabsorption of electrolytes and water from blood to the aqueous humor, and decreased prolactin secretion has been strongly linked with seasonal affective disorder, we propose that observed derangements of prolactin could possibly be secondary to the lowered intraocular pressure values. This might, in fact, be the case, since a hypothesis of increased dopamine function is not consistent with the observations of decreased locomotion and affective behavior in these patients.

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Initial Reaction and Subsequent Response to Antidepressants in Panic Patients

SIR: Reports have indicated that panic patients treated with tricyclic antidepressants or fluoxetine may have a worsening of their condition within the first week, which often causes them to drop out of treatment (1–3). In this report, we explore the possibility that this worsening may be explained by the higher sensitivity of some panic patients to antidepressants and that it may be used as a marker for response to a lower dose.

Twenty patients with *DSM-III-R* diagnoses of panic disorder with or without agoraphobia who had been admitted to the anxiety disorders program at the University of California, Los Angeles, were treated randomly with fluoxetine or desipramine. We used an open-label, flexible-dose design. Doses of desipramine ranged from 5 to 250 mg/day, and doses of fluoxetine ranged from 5 to 40 mg/day.

We observed that several of the patients had strong initial increases in anxiety and panic symptoms during the first week of treatment. They had at least a 25% increase in their scores on the Hamilton Rating Scale for Anxiety and the Four-Dimensional Anxiety Scale (4), and they also had significant increases in the number and intensity of panic attacks. A total of 13 patients, six of the 10 patients treated with fluoxetine and seven of the 10 patients treated with desipramine, had this initial reaction. However, by the tenth week of treatment, 10 of these 13 patients had a dramatic response, with no major panic attacks and significant decreases in scores on the two anxiety scales. They were judged much improved on the Global Assessment Scale. Only three of the patients who had the initial reaction were eventually unable to tolerate the treatment. The seven patients who did not have the initial reaction required larger doses of their medications. Four of these seven failed to respond.

The improvement was similar in both treatment groups as observed on the self-rated and the clinician-rated measures. These findings suggest that both fluoxetine and desipramine may be effective antipanic agents. It also suggests that the initial increase in anxiety and panic may be a possible marker for the subsequent response to lower doses.

Some of the possible explanations for our findings are heightened initial neurotransmission coupled with presynaptic or postsynaptic sensitivity (5), presence of higher blood levels at lower doses of medicine, or heightened individual sensitivity.

It is often difficult to distinguish the initial increase in panic from the increase in anticholinergic or serotonergic side effects that may be caused by these drugs. Our findings, although interesting, are disputable because of the small sample, open-label design, and presence of secondary depression in some patients. A larger, more carefully designed study is needed to clarify questions raised by this protocol.

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Manic Illness Presenting With Physical Symptoms

SIR: Mania, like its sister, depression, can present with a sometimes distracting variety of physical symptoms (1–3), such as neck pain, sinus pain, and abdominal cramping. I undertook a chart review, using a checklist covering musculoskeletal, gastrointestinal, vestibular, and paranasal sinus areas and noting physical complaints documented in progress notes, of 302 patients that I had treated over a 12-year period in the psychiatric division of a general hospital. These 302 patients had been given discharge diagnoses of mania and also met the *DSM-III* criteria for mania. Cases of mania secondary to endocrine or CNS disease were not included. The symptom checklist also included a rating of response of the physical symptoms to the treatment for mania. This retrospective review had the limitations of lack of control subjects and absence of rigorous definition of symptoms. Nonetheless, it revealed a surprisingly high prominence and diversity of symptoms.

Of the 302 hospitalized manic patients, 178, or 58.9%, were female, and the mean age when they first sought treatment was 32 years (range=16–68 years). One hundred forty-three patients (47.4%) showed a major physical symptom during the episode of mania. For 102 patients a physical symptom constituted the primary complaint. Of the 302 patients, 232 had a first-degree relative with mood disorder.

Muscle pain, headache, neck pain, back pain, and chest wall pain were the most common physical symptoms; they appeared in 103 of the 143 cases. Some patients were using sedatives or analgesics for such pain. Many had undergone extensive study before referral to the psychiatrist. Typically, the patients showed a manic pattern of agitation and pressured speech in discussing these physical symptoms, a pattern that can divert clinical attention away from the symptoms themselves. Digestive symptoms such as soreness, burning, or cramping in the abdomen or loose stools were next most common; they appeared in 101 of the 143 patients. A feeling of discomfort, fullness, or exaggerated satiety was present in 49 of these 101 patients.

Seventeen patients had complaints of dizziness or sensations of head motion, nausea, motion sickness upon walking, moving, looking down, or watching traffic, or nausea when watching strobe lights. Patients typically are frightened by these symptoms, and the clinician is challenged by their obvious origin in brain dysfunction. Perhaps such symptoms represent exaggerated vestibular sensation activated along with the autonomic dysfunction seen in mania.

Twenty-nine patients reported draining, fullness, or pain in the paranasal sinuses. Of these, 21 were using sympathomimetic preparations that can aggravate or precipitate manic episodes. Characteristically, these patients were intensely dysphoric and specifically fearful of stopping their sinus medications. Typically, the use of lithium to control the mania also controlled the sinus symptoms, after which the aggravating medication could be removed.

The prominence of these physical symptoms along with mania can distract the patient and physician from initiating the use of lithium salts and other treatment for mania. The usual and typical course is that the physical symptoms promptly remit as the mania comes under control with specific treatment. In a considerable fraction of the cases I have described, distraction of care toward attempts to relieve the physical symptoms had delayed commencement of specific treatment for mania.

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Use of Unproven and Unapproved Drugs to Treat Cocaine Addiction

SIR: Although there have been reports (1, 2) of desipramine's *statistically* significant efficacy in the outpatient treatment of cocaine addicts, other investigators (3, and unpublished manuscript by I. Arndt et al., 1989) have found no differences between desipramine and placebo with respect to patients' craving for cocaine, retention of patients in treatment, and their use of cocaine during treatment. More important clinically, desipramine has not been demonstrated to improve retention of patients in outpatient treatment or decrease rates of relapse. Thus, *clinically* significant efficacy of desipramine in the treatment of cocaine addiction has not yet been demonstrated. Moreover, although there have been no reports of cardiovascular problems by cocaine addicts receiving desipramine in controlled studies, tricyclic antidepressant medications may affect cardiovascular function by causing postural hypotension or slowing cardiac conduction (4).

Given that desipramine is approved and available for treatment of depressive syndromes, precautions are advised for physicians who prescribe desipramine or other as yet unproven medications (e.g., imipramine, carbamazepine, and amantadine) for cocaine addicts without the symptoms and clinical course of a major depressive syndrome or other conditions for which a drug is approved. In these situations one may wish to use measures similar to those used by clinical researchers testing an investigational drug: writing a treatment protocol, having the protocol reviewed and approved by an institutional review board, and using informed consent procedures which state to prospective volunteer patients that the drug is so far unproven for treatment of cocaine addiction and which list possible adverse reactions.

Further research on desipramine and other pharmacological agents is needed in order to better determine their efficacy in the treatment of cocaine addiction, which is presently an important public health problem.

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Effects of Sedatives and Neuroleptics

SIR: I found "Time Course of Antipsychotic Effects of Neuroleptic Drugs" by Paul E. Keck, Jr., M.D., et al. (1) to be a blockbuster. It is the first anti-antipsychotic article I've seen in many years.

There is a seeming contradiction: "The efficacy of neuroleptics . . . has been established beyond doubt" versus "The same overall degree of improvement was observed . . . with all the agents tested" and "When a neuroleptic was compared to a sedative . . . the sedative demonstrated efficacy similar to that of the neuroleptic during the first day . . . and through 4 weeks . . . of treatment."

Many questions arise in this admittedly naive clinician. Has our clinical judgment about the efficacy of antipsychotics been a fixed, encapsulated, delusional perception, systematized by the dopamine hypothesis? What are the implications for the dopamine hypothesis? If there is no difference in outcome in a month, how about 2 months, or 6, or a year, or a lifetime? Do sedatives prevent relapse as well as antipsychotics do? Are we back to square 1 in antipsychotic psychopharmacology?

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Decisions in Psychopharmacologic Treatment

SIR: I was immediately taken by the letter from Lakshmi N. Yatham and associates (1). Although the intent of the letter was clearly to raise interest in exploring the safety and efficacy of combining carbamazepine with monoamine oxidase inhibitors (MAOIs), I believe the letter raises a far more daunting question: what are the appropriate algorithms for making clinical decisions in psychopharmacologic treatment of the elderly? The issue of carbamazepine serum level and its variability in the presence of MAOIs is only one of a number of questions regarding efficacy and toxicity in the authors' case report. Is carbamazepine an appropriate first-line treatment for poststroke depression? Should three psychoactive pharmaceuticals be used during the first step of a treatment strategy for this disorder (2)? Is the carbamazepine and lithium combination safe (3)? Is the blood level of carbamazepine the only relevant risk factor with respect to the pharmacodynamic impact of carbamazepine and phenelzine or other MAOIs in combination (i.e., what are the risks of delirium, postural hypotension, and hypertensive crisis, in particular)? Does carbamazepine, with its tricyclic structure not dissimilar to that of tricyclic antidepressants, adversely potentiate the risk of hypertensive crises when it is used concomitantly with MAOIs? Moreover, was the combination of carbamazepine and phenelzine in this case necessary, as phenelzine alone or no treatment might have worked equally well?

By my estimate, a minimum of 12 weeks would have been necessary to achieve remission in this case. Was the clinical algorithm, described by the choices made for the patient, the most efficient in time and the least toxic in risk, given the initial diagnostic impression? With the myriad agents and the endless combinations of such agents now available, the potential risks of any one combination are overwhelmed by the need to devise and test well-defined algorithms of clinical decision that maximize the efficiency and minimize the risk throughout the course of treatment.

The case of Ms. A clearly demonstrates the need to review and reevaluate the willingness to prescribe atypical agents and combinations of agents. Decision-analytic research should be brought to bear on this complex subject (4).

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Hopelessness as a Predictor of Suicide

SIR: It was with great interest that I read the article by Aaron T. Beck, M.D., and associates (1) on the relationship between hopelessness and suicide. They attempted in this article to emphasize hopelessness as one of the central issues the clinician needs to appreciate when assessing the potential for suicide in depressed outpatients. They addressed the question of how we can better identify the depressed individual who is eventually going to commit suicide, which is obviously important, as up to 10% of depressed hospitalized patients will eventually commit suicide (2). Although this is a high prevalence, it is low enough to mandate that the sensitivity and specificity of a screening test to predict suicide be high in order to detect with reasonable certainty the risk for an individual patient (3). Furthermore, the aspect of a test's capabilities that the clinician will be most interested in is the positive predictive value (3).

In the study by Dr. Beck and associates, the Beck Hopelessness Scale seemed to have fairly good sensitivity (94.1%), but specificity was lower (41.0%) with a cutoff score of 9. Furthermore, a high-risk score on the hopelessness scale was 11 times more likely than a low-risk score to predict suicide. These numbers indicate that this is a very good instrument for assessing risk of suicide. However, due to the low prevalence of suicide in this study, the yield when this instrument was applied was only 1.4%. In other words, only one or two patients of every 100 identified through this instrument will eventually commit suicide in the follow-up period used by Dr. Beck and associates.

Furthermore, when this article compares the efficacy of this instrument in assessing suicide risk relative to other factors, the reader needs more information to be able to calculate the positive predictive value. As an example, we are not given the exact numbers of male patients and alcohol-related diagnoses. If one-third of the total sample are men, the positive predictive value is 1.4%, and if we assume that alcohol-related diagnoses are as common in the whole sample as among the suicide victims, the positive predictive value is 0.9% for the patients with alcohol-related diagnoses. Consider, though, that if the prevalence of alcohol-related diagnoses in the sample is 20% instead of 29.4%, the positive predictive value is 1.3%. What this emphasizes is that the hopelessness scale with a cutoff score of 9 may have an ability similar to that of a diagnosis related to alcohol and of sex to predict who among the patients we see today will be among the 10% who eventually commit suicide. Our ability to predict who is going to commit suicide clearly depends on what type of patient population we are looking at. Comparing one predictor with another can, therefore, be misleading unless the full sample in which these measures are used is described with respect to all significant variables.

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Dr. Beck and Dr. Steer Reply

SIR: Dr. Tomasson makes two relevant observations with respect to our report on the prediction of suicide on the basis of the Beck Hopelessness Scale. First, in answer to the comments on positive predictive value, Baldessarini et al. (1) have previously presented examples of how even instruments with high sensitivity yield very low positive predictive values when the incidence of the phenomenon under study is low. We recognize the inherent base rate problem with the positive predictive value for the hopelessness scale (2).

While we subjected our data to the conventional statistical procedures relevant to sensitivity, specificity, and positive predictive value, it should be noted that these procedures are conventionally used to index a test's ability to identify a disease that is already present. They are not generally used to assess a test's ability to forecast either the later development of a disease or ultimate death from that disease.

A more appropriate index of the value of the Beck Hopelessness Scale is the concept of "relative risk." The scale was able to isolate a high-risk group that was 11 times more likely to commit suicide than the rest of the patient sample. In this respect, the prediction of eventual suicide is analogous to the prediction of death from heart disease or cancer from heavy smoking. Studies in those areas focus on risk factors rather than on positive predictive value.

Second, Dr. Tomasson expresses concern about our lack of data with respect to the combinations of other demographic variables in forecasting suicide. Our analysis reported only the findings based on the hopelessness scale, since the study was intended to be a cross-validation of our previous results with hospital inpatients, in which the only variables that predicted ultimate suicide among those with suicidal ideation were the Beck Hopelessness Scale (3) and clinical ratings of hopelessness (4). Further analysis of our outpatient data has provided preliminary evidence that other factors, such as low self-concept, previous suicide attempts, severity of suicidal intent, and a history of alcoholism, also make a contribution to future suicide. However, these findings will have to be validated in another study.

The important clinical question is, How can these findings best be applied in clinical practice? We believe that the more than 90% success rate in forecasting ultimate suicide of both inpatients (3) and outpatients indicates that the Beck Hopelessness Scale may help clinicians identify patients who are at highest risk for eventually committing suicide and, consequently, focus treatment on suicide prevention. Also, an elevated score can prompt the primary care physician to delve further into the patient's symptoms and personal problems and then make a psychiatric referral if indicated.

Since hopelessness can be reversed by psychosocial or pharmacological interventions (5), its identification may be life-saving for the individual patient. Further, high scores on the Beck Hopelessness Scale have been shown to predict future *nonfatal* suicide attempts by patients who have been hospitalized previously for attempted suicide (manuscript by A.D. Brittlebank et al., 1990). Thus, the scale may have a broad applicability. It may also be a useful tool for assessing the need for hospitalization, involuntary commitment, and suicide precautions.

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Personality Traits and Ethnic Background

SIR: In their article on transethnic adoption and personality traits (1), Wen-Shing Tseng, M.D., and associates argued that there are personality traits learned early in life which are specific to and characteristic of a culture—in this case, Japanese. Unfortunately, the design of the study only suggests this. One cannot rule out the effects of the subjects' location (the China Returned Orphans Settlement Promotion Center) on the respondents. For example, could they have been influenced to cite different (non-Chinese) traits because of a desire to confirm the "Japaneseness" of their spouses and, thus, enhance acceptance of them?

The authors stated that the non-Chinese traits cited by the spouses "can be matched with the traits that we have described as characteristic of the Japanese character in general." Since there are no references in the article to this, where did the authors describe them? This is important, since it is the crux of the authors' argument.

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Dr. Tseng and Associates Reply

SIR: Dr. Jensen is correct in his concern that, when the Chinese spouses in our study were asked whether they had noticed any personal characteristics about their spouses who were Japanese war orphans, they might have cited certain traits because of a desire to confirm the spouses' "Japaneseness." This point was taken into consideration when the interviews were conducted. The questions were phrased carefully by asking whether they had noticed any traits of their spouses that contrasted with those of (Chinese) people in general. They were not asked to describe any "Japaneseness" they found in their Japanese war orphan spouses. As a result, various traits were reported, which included some with "negative" value, such as "severely disciplines children," "acts fast/impulsively," and "has a temper." Therefore, it is our opinion that the responses were not affected by the couples' enrollment in the China Returned Orphans Settlement Promotion Center at the time of the interview.

After the article was published, 50 Japanese-orphan and Chinese-spouse couples who decided to stay in China were interviewed in China by the same method. A similar result was obtained among these couples who have no desire to be considered Japanese. Therefore, the influence of the desire for conformity on the interview can be considered minimal. As a part of the overall project, all the Japanese orphans and their Chinese spouses were administered personality questionnaires. The results of these objective measurements will be available in the future to compare with the results from the subjective interviews.

As for the second question concerning the description of Japanese characteristics, the information was based mainly on the studies by Doi and by Lebra, cited in references 17 and 18, respectively, in the article. Additional resources include the works of Benedict (1), Caudill and Weinstein (2), and Lebra and Lebra (3).

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Seasonal Variation in Bulimic Symptoms

SIR: In his letter on light therapy for seasonal bulimia (1), Raymond W. Lam, M.D., F.R.C.P.(C), asserted that "winter worsening of mood and bulimic symptoms is commonly seen in bulimia nervosa." Perhaps Dr. Lam has jumped the gun in using the term "seasonal bulimia" on the basis of a single case report in which a clinically insignificant change in frequency of binges from 12 to six times per week occurred as a result of the patient's exposure to bright light. The patient he described seemed to suffer from seasonal affective disorder in addition to bulimia. A more powerful finding would be that of seasonal changes in eating behavior (binges) as well as in core psychopathologic attitudes and beliefs related to weight and shape in a patient free of any mood disturbance.

To account for winter worsening of bulimic symptoms in bulimia nervosa, Dr. Lam listed a number of important psychosocial variables. These factors, in addition to a mood state that responds to light therapy, may be important in influencing the natural history of bulimic symptoms. Investigators have shown that there is a waxing and waning of binge frequency over time in most patients (2). Dr. Lam suggested that serotonergic dysfunction has been implicated in the carbohydrate cravings found in patients with seasonal affective disorder. It is interesting to note that a recent study (3) has shown that bulimic patients have less seasonal variation in platelet serotonin uptake than normal control subjects.

We have recently completed a retrospective pilot study of seasonality of symptoms in a group of 165 patients with bulimia nervosa admitted to an eating disorder day hospital program over a 5-year period. At the time of admission, each patient was assessed in terms of demographics, eating attitudes and behavior, eating and weight history, depression, anxiety, general psychopathology (including dimensions of personality and suicidality), and social adjustment. Subjects were retrospectively assigned to one of four seasonal groups on the basis of date of admission. Analysis of variance indicated differences only on age (mean±SD: summer, 27.83±9.7 years; fall, 23.64±4.3 years; $p<0.02$), social adjustment rating (mean±SD: spring, 2.74±0.5; summer, 2.32±0.6; $p<0.02$, spring group more maladjusted), and scores on the anxiety and borderline scales of the Millon Clinical Multiaxial Inventory (4) (mean±SD for anxiety scale: spring, 100.85±5.2; winter, 83.90±19.5; $p<0.02$; for borderline scale: spring, 87.15±13.6; winter, 72.95±13.1; $p<0.04$). There were no differences across seasons on measures of binge frequency, eating attitudes, or depression. Elevated borderline scale scores in the spring could theoretically reflect increased impulsivity secondary to lowered 5-hydroxyindoleacetic acid levels in spring (5).

Firm conclusions regarding seasonality in bulimia cannot be drawn from such a study or from a single case report. It is possible that there are subgroups within a heterogeneous population of bulimic patients who demonstrate clinically significant seasonal shifts in binge frequency and in core psychopathologic symptoms independent of any mood disturbance and for whom light therapy could be selectively prescribed. We are now conducting a prospective study examining seasonal patterns of symptoms in a group of bulimia nervosa patients with and without mood disorder. We hope that this study will be able to establish whether seasonal bulimia is a true clinical entity.

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ALLAN S. KAPLAN, M.D., F.R.C.P.(C)
ROBERT D. LEVITAN, M.D.
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Dr. Lam Replies

SIR: Drs. Kaplan and Levitan are certainly welcome to question my provocative use of the term "seasonal bulimia." Since no one else has used the term, I simply took the prerogative to use it to describe seasonal exacerbations of bulimic symptoms. They are also correct in stating that their interesting data do not rule out a subset of "seasonal" bulimic patients. A similar situation occurs with seasonal affective disorder, where a clinically distinct subset is obscured when one looks at seasonal variability across a heterogeneous depressive sample.

Because mood disturbance is so common in bulimia, however, I would not exclude concomitant seasonal mood changes in any definition of seasonal bulimia. It is possible that the patient I described coincidentally had seasonal affective disorder in addition to bulimia, but recent evidence suggests a high prevalence of seasonal mood symptoms in bulimia. In a study using the Seasonal Pattern Assessment Questionnaire (1), a self-rated retrospective questionnaire developed for use in seasonal affective disorder, bulimic patients were more similar to patients with seasonal affective disorder than to a normal control group in describing seasonal mood, weight, appetite, and eating patterns (2). In our study of an unselected group of 26 bulimic patients who completed the Seasonal Pattern Assessment Questionnaire, 46% met the case-finding epidemiologic criteria for seasonal affective disorder, as defined by Kasper et al. (3), compared to 4.3% of a randomly selected community sample ($\chi^2=14.0$, $p<0.0002$) (4). This finding is unlikely to be due to independent segregation of seasonal affective disorder and bulimia. Another study found that 41% of 319 overweight women recruited for a diet study had regular seasonal weight changes. This seasonal subset reported an average 13-lb weight gain in fall/winter, associated with carbohydrate craving, and an average 11-lb weight loss in spring/summer, a pattern similar to that found in patients with seasonal affective disorder (5). These studies suggest that seasonal mood and appetite changes may indeed be linked to changes in eating that can exacerbate bulimic symptoms. I will certainly look forward to more systematic studies from Drs. Kaplan and Levitan, our group, and investigators in other centers who are exploring the issue of seasonality in bulimia nervosa.

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RAYMOND W. LAM, M.D., F.R.C.P.(C)
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Multiple Personality Diagnostic Criteria

SIR: "Structured Interview Data on 102 Cases of Multiple Personality Disorder From Four Centers" by Colin A. Ross, M.D., F.R.C.P.(C), and associates (1) indicated that multiple personality disorder has a stable, consistent set of features, that it may be diagnosed with a structured interview in many cases, and that "once a systematic inquiry for multiple personality disorder is made part of the routine diagnostic assessment . . . the disorder will no longer be thought to be rare." In addition to a structured interview, the authors proposed a third diagnostic criterion: the presence of at least one of four indications of amnesia.

But why would the diagnosis of multiple personality disorder ever require such systematic inquiry? If a patient truly fulfilled the basic diagnostic criteria and was in fact alternating among different personalities, how could one miss such a thing or mistake it for anything else? While the *DSM* text does include some cautionary information in this regard (e.g., that the presenting personality often does not know of the other personalities), the diagnostic criteria as they now stand do not suggest that the multiple personalities themselves ever stay out of sight, pass for each other, or are otherwise not immediately recognizable. Perhaps criterion A should be revised to state, "The existence within the person of two or more distinct personalities or personality states (each with its own relatively enduring pattern of perceiving, relating to, and thinking about the environment and self), *recognition of which often requires systematic inquiry.*"

Now, against this proposal, it may be argued that all diagnoses require systematic inquiry. But the problem is that criterion A in *DSM-III-R* together with stereotypical expectations for this disorder mislead us to expect that the alternating personalities will be readily recognizable, when in fact there may be special obstacles to their recognition, such as the presenting personality's ignorance of the other personalities.

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KENNETH A. NAKDIMEN, M.D.
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Dr. Ross Replies

SIR: I thank Dr. Nakdimen for taking the time to comment on issues raised by our article on multiple personality disorder. I have a few comments in reply.

A structured diagnostic interview should not be required for making any psychiatric diagnosis. We said that a systematic inquiry is required in order to make the diagnosis of multiple personality disorder for several reasons. As Dr. Nakdimen points out, such an inquiry is required for all diagnoses. More important, the fact that multiple personality patients spend an average of 6.8 years in the mental health system prior to diagnosis of their dissociative disorder (1, 2), and are often misdiagnosed as suffering from schizophrenia, suggests that standard clinical interviews are insufficient. We wanted to emphasize that there are specific questions about amnesia, child abuse, auditory hallucinations, and the sense of another identity inside which should be part of all diagnostic assessments and without which multiple personality is unlikely to be detected. Kluft (3) has pointed out that multiple personality usually presents in a covert fashion and is missed if such inquiries are not made.

I disagree with the proposed addition to *DSM-III-R* criterion A. It implies that a less systematic inquiry might be sufficient for other diagnoses. As a notation in the *DSM-IV* text on multiple personality, it would be worth mentioning that a specific inquiry for the secondary features of the disorder is necessary. These could be described in the text.

Hopefully, by the time *DSM-V* comes along we will be able to further operationalize the diagnostic criteria for multiple personality so that we can better differentiate complex cases related to extreme trauma from milder and nontraumatic forms of multiplicity and from borderline personality disorder. At present the major barrier to making the diagnosis is probably errors of omission in the standard diagnostic interview and mental status examination. The standard mental status examination of auditory hallucinations should include questions about other Schneiderian intrusions attributed to the voices by the patient and the gender, name, "personality" characteristics, and affective charge of each voice; localization of each voice internally or externally; and an attempt to indirectly engage the voices in rational conversation by using the presenting part of the patient as an intermediary. This last technique should not be used indiscriminately. The relationship between voices and blank spells needs to be asked about. Such questioning should be part of standard clinical interviews in emergency departments, on the wards, and in outpatient settings.

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Further Discussion of Article on Prodromal Symptoms in Panic Disorder

SIR: I am writing to question the nature of the Letters to the Editor section in the *Journal*. Submitted articles undergo peer review. The criteria include posing and answering questions in a fashion that respects logic, data, common experience, and past research. Such criteria appear to be waived when it comes to letters replying to criticism.

Letters often take issue with an article, and the authors respond. However, these replies are often simply attempts at damage control and further obfuscate the issues.

A case in point is my letter (1) which suggested that an article by Giovanni A. Fava, M.D., and associates (2) had certain invalidating deficiencies: 1) the authors misconstrued the notion of "controlled" studies; 2) their data rested entirely upon interviews by a single nonblind psychologist; 3) their so-called control group was only cosmetic, because the issue was the course of agoraphobia, not the difference between agoraphobic patients and normal persons; 4) their reliability study suffered from having too small a number of subjects; 5) they misattributed to me a statement that patients are "confident and energetic" before their first panic attack; 6) they found a high prevalence of antecedent hypochondriasis (17 of 20 patients) and possibly misinterpreted spontaneous panic attacks as hypochondriasis; and 7) it seemed no more logical to suggest that the belief that panic attacks engender agoraphobia is an "effort after meaning" than to suggest that the belief that agoraphobia engenders panic is an "effort after meaning."

In their response (3), Dr. Fava and associates did not constructively deal with my questions. How can my antique observation that 50% of panic patients have childhood separation anxiety be misconstrued as showing that my "views on the pre-panic patient are changing"? My observations clearly did not imply that before the onset of panic the patients were feeling anxious. Supporting their viewpoint by misquoting me is not acceptable.

Dr. Fava and his colleagues stated, "We would like to reassure Dr. Klein that we are able to discriminate between hypochondriasis and panic attacks." It seems unnecessary to be forced to point out that such self-serving statements have no scientific weight and do not belong in an empirically based discussion. Such rhetoric also completely ignores why I suggested that they may be confusing hypochondriasis with panic attacks. Dr. Fava and associates reported an atypically high incidence of hypochondriasis preceding the onset of phobic avoidance. This remains unexplained and may account for their report.

In order to support the claim that hypochondriasis, phobic anxiety, etc. are prodromal for panic, the rater must be able to distinguish these purported "prodromal symptoms" from actual panic symptoms. There is no scientific evidence in either the authors' report on their study or their letter that their nonblind rater could make this distinction reliably or objectively.

The very act of publication in an academic journal bears a certain cachet. If a replying letter fails to deal with the issues, as I suggest Dr. Fava and associates' reply did, then it should be returned after the review process to be either improved or forgone.

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DONALD F. KLEIN, M.D.
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Dr. Fava and Associates Reply

SIR: In his first letter commenting on our article, Dr. Klein raised a number of methodological issues with respect to our study on prodromal symptoms in panic disorder with agoraphobia. We believe we offered an adequate reply to those issues, obviously within the space constraints of the *Journal*.

We have the following comments on Dr. Klein's further specific points. 1) We stated that our study was methodologically superior not because it was controlled but because we used a detailed, semistructured research interview with cross-checking of relatives (1) and we postponed the interview until the acute disturbance had passed, since, as Furlong commented in his letter about our article (2), "It is only with both increasing exposure to phobic avoidances and some review of their previous behavior that these patients become aware that their avoidances are not natural or inevitable." 2) In a retrospective study on prodromal symptoms, the rater cannot be blind, since he or she has to determine the onset of the full-blown disorder (in this case, the first panic). 3) The control group was not "cosmetic"; it was designed only to exclude the possibility that our instrument might yield false positive results, which we had found in other studies on normal or medically ill subjects that used other scales. 4) The separate reliability study had a small number of subjects (N=7); that, however, was proportionate to the number (N=20) in the study. There was 100% agreement between the psychiatrist and the medical psychologist about the time of onset of the first panic attack. 5) If we misinterpreted Dr. Klein's view of the pre-panic patient, we apologize. However, if patients do not feel "quite well" before their first panic attack, how do they feel? The reference to separation anxiety in childhood does not clarify this point. 6) The likelihood of misinterpreting spontaneous panic attacks as hypochondriasis was decreased by the precise definitions of these conditions in our research interview (1) and by separate assessment of five dimensions of abnormal illness behavior (worry about illness, hypochondriacal beliefs, thanatophobia, disease phobia, and bodily preoccupation). These dimensions were derived from an instrument (Kellner's Illness Attitude Scales) that had revealed, when it was administered during the acute phase of panic disorder and after its treatment, a decrease in hypochondriacal fears and beliefs (3), as observed clinically by Dr. Klein. Prior to our study, the issue of antecedent hypochondriasis had eluded systematic investigation. We view hypochondriasis in panic and agoraphobia as a complex clinical problem, only in part secondary to panic attacks, as we have discussed in detail in a phenomenological paper (4). 7) The issue of "effort after meaning" was clarified in terms of life events research.

Dr. Klein is dissatisfied with our published response to his letter and calls for a closer editorial review of such correspondence. Unfortunately he fails to mention a crucial element in the critical evaluation of the contents of scientific journals—the reader. Unlike Dr. Klein, we have confidence in the judgment of the *Journal*'s readers and are certain that in their assessment of our differences they will take into account the fact that our having the last word here gives us a certain psychological and practical advantage. We further suggest that Dr. Klein perhaps attributes an importance to our study that we should be hesitant to accept. It was only a preliminary investigation of a small sample of Italian patients, and it awaits independent and more extensive replications. However, it did challenge a "dogma" (the primacy of panic in agoraphobia), and this may be what worries Dr. Klein so much.

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More on Psychotherapy Training During Residency

SIR: We greeted the model curriculum for psychotherapy training during residency developed by the joint task force of the Association for Academic Psychiatry and the American Association of Directors of Psychiatry Residency Training (1) with enthusiasm and appreciation for a job well done. The curriculum is comprehensive and practicable and fulfills the goals and objectives that are so carefully and thoughtfully articulated at the beginning of the article.

However, we were distressed to read the "curriculum for minimum training" that was also presented in the article. We felt that it undermined the strength of the argument for the model curriculum and suggested that, in effect, a little knowledge and minimal training in this area are equally acceptable. The task force offered the minimum curriculum for programs "with limited resources or with such a strong commitment to other areas of psychiatry that few resources are directed to psychotherapy training."

It is our view that the principles underlying the rationale for the unabridged model curriculum cannot be taught effectively in many residencies as they now exist, and we seriously question the wisdom of endorsing the idea that this can be done concisely or achieved with a minimum of effort, as in the curriculum for minimum training. The authors cannot have it both ways—and for that matter, neither can residency training programs or the Residency Review Committee in Psychiatry. Programs are to be expected to provide in-depth training in psychodynamic psychiatry that enables the psychiatrist of the future to be deeply and effectively informed about psychodynamics, or they are not.

Our thinking about this can be summarized as follows.

1. The field of psychiatry is burdened by uncertainty and ambiguity. While we are making headway in resolving this, it is, regrettably, very slow and there is still much to be clarified.
2. The field has been further burdened by its trendiness and tendency to oversimplify the issues. Whenever a particular orientation comes into favor, there is a relative disregard for alternative explanations.
3. Balanced integration of the biological, the psychological, and the social is in practice extraordinarily challenging, despite frequent assertions to the contrary. Departments and programs tend to be strongly oriented in one direction or another, and the task of maintaining a balance among the faculty is unendingly demanding.
4. Just as biological psychiatry and pharmacotherapy may have been underrepresented in some departments in the past, we are moving dangerously close to the restricted practice of psychodynamically informed psychiatry in departments now principally committed to a basic science orientation.
5. The academic leadership of psychiatry has an obligation to acknowledge what is still uncertain in the field, to respect the heterogeneity of the prevailing viewpoints, and to avoid the surrender of important principles out of concern for short-term practicality. Where resources in a department are limited, we must assert the need to enrich them. Where they are committed in an unbalanced way, we must work toward a balanced approach.

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GEORGE FISHMAN, M.D.
WILLIAM GREENBERG, M.D.
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Boston, Mass.

Comments on Review of *Male Homosexuality*

SIR: In his review of my book *Male Homosexuality: A Contemporary Psychoanalytic Perspective* (1), Robert Paul Cabaj, M.D., made many observations that were incorrect and misleading.

He stated, "Almost nothing is said about homophobia." In fact, homophobia was discussed throughout the book. I hypothesized that the absence of greater rates of psychopathology despite virulent discrimination suggests an "increased capacity for coping with adversity" in many homosexual people. Many clinical vignettes illustrated homophobia and a study of its effects on medical personnel was summarized.

Dr. Cabaj commented, "The author goes to great pains to disassociate homosexuality and mental illness early in the book but then, perhaps unwittingly, defeats his goal in part two by describing male homosexuals in various diagnostic categories, focusing on the borderline and primitive conditions." Actually, in *Male Homosexuality* I did the opposite of what Dr. Cabaj suggested. I compared homosexual, heterosexual, and bisexual individuals at various levels of character integration. I elected to discuss the entire range of character pathology routinely encountered in office practice. I did not focus on the borderline syndromes to a greater degree than the higher-level character neuroses. Dr. Cabaj observed, "It will take a sophisticated reader not to link homosexuality and these diagnoses." I assumed that the audience for whom I wrote my book, the readers of this journal, would indeed be sophisticated about clinical matters. Dr. Cabaj implied that mental health professionals should be protected from exposure to complex ideas. This argument, if followed to its logical conclusion, constitutes a justification for censorship.

After misrepresenting my views about gender identity and sexual orientation, Dr. Cabaj erroneously placed me in the category of "clinicians who cannot fully grasp how members of the same sex can love and want to be sexual with each other." He suggested that I believe that "if a man wants to be sexual with another man he must be woman-like on some level." There is not a shred of evidence for these views in my book. To the contrary, a major theme was the necessity of not basing clinical inferences about adult gender experience and behavior entirely on the childhood history of such behavior.

Statistically significant associations between childhood cross-gender behavior and adult homosexuality have been reported by numerous investigators from various disciplines using diverse methods of study. I assume that Dr. Cabaj would have preferred me not to discuss this scientific work.

In addition, I gather that he would have wished me to omit psychoneuroendocrinology and psychoanalytic psychology, since he neglected to summarize my treatment of either area. Such key psychoanalytic concepts as unconscious homosexuality and paranoia were only two of many I discussed in detail. I also considered the contributions of such investigators as Freud, Money, Ehrhardt, and Stoller and many others.

In the light of contemporary social and intellectual conflict about both psychoanalysis and sexual orientation, a more scholarly and less biased review of *Male Homosexuality* than the one provided by Dr. Cabaj would have been welcome.

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RICHARD C. FRIEDMAN, M.D.
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Dr. Cabaj Replies

SIR: Dr. Friedman makes several comments about my review of his book. I would like to reply to the points he raises and add a few comments.

In general, I felt that the book was an excellent contribution to a new and growing group of works that are attempting to take a fresh, nonpejorative psychiatric and psychoanalytic look at homosexuality. Most contemporary writers on these issues emphasize the overwhelming role of homophobia in the developmental adjustment problems and emotional distress that may influence the expression of symptoms in gay men and lesbians (1–3). I feel that Dr. Friedman's limited review of internalized homophobia is a problem for the understanding of gay men.

The comparisons that Dr. Friedman makes of various levels of character integration did emphasize pathology. Since so many therapists currently practicing were brought up on the "pathological model" of homosexuality, the inference of pathology is very easy to make and needs direct, clear refutation. This is particularly true since Dr. Friedman stated in his book, "I emphasize the relationship between the onset of homosexuality and gender disturbance . . . . Prior to differentiation, when homosexual phenomena are pathological (from a psychoanalytic perspective), they are best conceptualized as symptoms of an underlying disorder (usually gender identity disturbance)" (p. 248).

I do not feel I misrepresented his views, since the quotation confirms his belief that there is a link between "femininity" and male homosexuality, a belief almost all analysts hold, based, I believe, on the inability to imagine that true homosexual love is exactly like heterosexual love, only aimed at a same-sex object choice. His conclusions seem odd, because he himself stated that only 30% of gay men had childhood gender disturbance concerns.

The discussion of these findings is very important but must be put in perspective. I did not comment on some parts of his book, which were excellent summaries of psychoneuroendocrinology and psychoanalytic psychology, because of space limitations.

I also failed to mention that he never defined homosexuality, stating, "Bisexuality, like homosexuality, is not explicitly defined in this book. I hope the meaning expressed by the term will be clear in the contexts in which it is used" (p. 127). This lack of definition leads to a confusion between homosexual behavior and homosexual orientation and may have contributed to some of the confusion in the book. Finally, although AIDS is not a disease of homosexuals, the devastating impact on the gay community and the effects on sexual expression should be noted in any modern study.

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Reprints of letters to the Editor are not available.

The Psychiatrist and the Juvenile Justice System

This report was drafted by the Task Force on Juvenile Justice Issues and revised by the Committee on Juvenile Justice Issues[1] *of the Council on Children, Adolescents, and Their Families. It was approved by the Board of Trustees in June 1990.*

The Task Force on Juvenile Justice Issues was convened in 1985 by the APA Council on Children, Adolescents, and Their Families. Its official charges were

1. to determine the availability of data on a) the extent of psychiatric problems in children and youth who are brought before the court, particularly those incarcerated in correctional institutions, and b) the extent to which appropriate diagnostic and treatment services are provided; and
2. to recommend to the council further specific studies and actions that would be appropriate to the findings.

This task force grew out of numerous inquiries to the council regarding the process of assessment of alleged offenders, the process of adjudication, concerns about incarceration of juveniles in adult facilities, concerns about the lack of rehabilitative services for juvenile offenders, concerns about the lack of psychiatric involvement in the juvenile justice system, and concerns about the inadequacy of data and research on all of these issues. In its deliberations, the task force decided to focus on the role of the psychiatrist in the juvenile justice system.

While the pendulum often swings from rejection of the rehabilitative and treatment model in corrections to recognition of the need for mental health clinical input, the importance of psychiatric involvement remains constant. The purpose of this report is to identify points in the juvenile justice system at which clinical intervention is desirable, to highlight some of the problems in meeting these needs, to recommend methods of overcoming the difficulties, and to address relevant training, research, and public policy issues.

Delinquency is a legal concept. A delinquent is a child who has been found guilty of an act that would be considered a crime if committed by an adult. Our current juvenile justice system has its origins in English common law, which held that children under the age of 7 could not be held accountable for criminal acts because they did not possess *mens rea,* i.e., guilty mind (1). In addition, the English chancery courts operated under the *parens patriae* doctrine, by which the king had responsibility for protecting the infants of the country. Whereas the chancery courts attended to the welfare of children who were abused, neglected, or abandoned, the establishment of the first juvenile court in Illinois in 1899 extended this assistance to children charged with violating the law.

There was considerable psychiatric involvement in the original juvenile courts. These psychiatrists included such pioneers as Adolf Meyer, E.E. Southard, Mary Jarrett, William Healy, Franz Alexander, and Augusta Bonner. Others who followed included August Aichhorn, Kate Freidlander, Anna Freud, Kurt Eissler, Bruno Bettelheim, Fritz Redl, John Bowlby, and Peter Blos. Their contributions consolidated the linkage between psychiatry and juvenile delinquency. Since the 1950s, however, there has been a waning of interest by psychiatry and psychiatrists in juvenile delinquency as a field of study and practice.

Significant changes within the juvenile justice system began to take place in the 1960s and 1970s, when a series of landmark court decisions ushered in the era of the equal rights movement for children and adolescents. Under the doctrine of *parens patriae*, courts were informal and legal counsel usually was not present. Due process, a cornerstone of the adult court system, was deemed unnecessary in the paternalistic juvenile court system. In the 1960s, however, civil libertarian lawyers complained that the juvenile justice system, through relaxation or absence of formal procedures, had inadvertently treated juvenile defendants more harshly than they would have been treated as adults in an adversarial system. To protect youth from arbitrary treatment, the Supreme Court decision *In re Gault* (2) established that juveniles must be afforded certain due process rights, such as notification of charges, the right to legal counsel, protection against self-incrimination, and the right to call and confront witnesses. Other court decisions followed and, with them, expansion of the legal rights of children against benign intervention by the state or by their parents (3).

In the 1970s the American Bar Association and the Institute of Judicial Administration initiated the Juvenile Justice Standards Project in an attempt to assess and reform the system. The project rejected the rehabilitative model and affirmed the precedence of family autonomy over state intervention except where juveniles' interests were inadequately protected without court involvement (4). Addressing the problem of status offenders (children who have committed such acts as truancy, running away, and disobedience to parents, which would not be deemed criminal if committed by adults), the standards recommended eliminating court jurisdiction over this group in favor of referrals to community-based services. In responding to the standards, APA reaffirmed psychiatry's role in the field of juvenile justice. APA advocated retention of court jurisdiction over status offenders and argued that the rehabilitation model should not be abandoned. Most recently, there have been further movements toward criminalization of the juvenile justice system, such as the waiver of serious juvenile offenders to adult courts and extension of capital punishment to juvenile offenders.

What is the appropriate involvement of the psychiatrist in the juvenile justice system? Vast numbers of juvenile offenders are being identified as emotionally, educationally, or mentally handicapped, as having histories of child abuse or substance abuse, or as suffering from medical and psychiatric disorders. According to statistics published by the House of Representatives Select Committee on Children, Youth, and Families (5), 40% to 70% of juvenile delinquents in secure facilities were found to have some form of handicapping condition. On the other hand, nationally only 36% of correctional facilities for incarcerated delinquents provide any psychiatric screening, and the role of physicians and educators in other parts of the juvenile justice system is even less apparent (5). The scope of the problem is underscored by the fact that in 1987, 25,024 children and adolescents were incarcerated in state-operated juvenile institutions but fewer than half that number were patients in state mental hospitals (6).

---

[1] The committee members were Edward H. Futterman, M.D. (task force chairperson), William M. Buzogany, M.D. (committee chairperson), Carolyn R. Haynie, M.D., Michael G. Kalogerakis, M.D., and Richard C. Marohn, M.D. Jeanne Spurlock, M.D., is staff liaison.

Given the large number of children in the system with psychiatric disorders, the need for psychiatric clinical input is immense. The clinician is most often asked for help in disposition and in provision of service. Whether a child enters the juvenile justice system or the mental health system may have more to do with minority status and socioeconomic status than with degree of psychopathology (7). Lewis et al. (8) stated, "Many seriously psychiatrically disturbed, abused, neglected black children are being channeled to correctional facilities while their white counterparts are more likely to be recognized as in need of help and directed toward therapeutic facilities." In some areas of the country, poor whites and other indigent minority groups have been reportedly overrepresented in the juvenile justice system. Whether a child enters the mental health system or the juvenile justice system and is labeled "sick" or "bad" influences the services that the child and the child's family receive.

The youth's first brush with the juvenile justice system is with an arrest. The arresting officer may or may not have a youth guidance component available to help decide which children need to go to court, which may need some community intervention, and which may need to be referred for clinical services.

When the youth is in the preadjudication phase of the juvenile justice process, it is often a probation officer who makes the decision about whether to bring the child to court or to divert the youngster to a community resource. The probation officer should be provided with information about the availability of diagnostic and treatment services in order to help the officer make these decisions. While it cannot be expected that every court will have a clinical team available on site, such services can be provided by existing clinical resources, which may be hired on a contractual basis, provide rotating coverage, be available on a case-by-case basis, or visit periodically as a mobile team.

The Committee on Juvenile Justice Issues contends that psychiatric evaluation should be available whenever needed by a probation officer or a judge and that such evaluators should be prepared to help with recommendations about disposition. The evaluation may be in the form of a screening for need for further services, in-depth psychiatric interview of the child and the family, complete interdisciplinary assessment (including physical, psychological, developmental, family, educational, and social evaluations), or X-ray, EEG, CT scan, and laboratory tests.

Psychiatrists may be called on at any point in the process—prevention, early intervention, diversion, community-based services, institutionally based services, or aftercare. Depending on the point of contact, the psychiatrist may provide assessment, evaluation, consultation, supervision, training, or direct patient care. Psychiatrists need to reorient themselves to think of antisocial behavior as a presentation of a potential diagnostic and treatment problem of a psychiatric nature. Too often, delinquents are automatically dubbed as conduct disordered without consideration of other diagnostic categories. On the other hand, numerous studies have uncovered a wide variety of psychiatric disorders in delinquent youth. These include affective disorders, attention deficit disorders, psychosis, substance abuse, borderline personality, and other personality and learning disorders (9–12 and unpublished findings of R.H. Rosenthal et al.).

Many young offenders are being waived to adult courts because of their involvement in violent crimes. Waiver may preclude appropriate treatment in adolescent facilities. Since the prevalence of psychiatric disturbance among violent delinquents is high (12 and unpublished data of Rosenthal and W.C. Myers, 1990), this committee recommends that each youngster undergoing waiver receive a full psychiatric diagnostic and treatment evaluation.

There is ample evidence that a significant number of delinquents incarcerated in juvenile facilities suffer from psychiatric disorders, such as attention deficit hyperactivity disorder, depression, psychosis, and learning disabilities, and are often indistinguishable from youth on mental health wards except for racial and socioeconomic differences. Therefore, the committee recommends that all correctional facilities for juvenile delinquents have available comprehensive psychiatric diagnostic and treatment services and the means to identify neurological impairments, learning disorders, and family psychopathology. While such services may not be present in many communities, the committee recommends that psychiatric training programs form liaisons with correctional schools and make available psychiatrists, neurologists, pediatricians, psychologists, and educators to evaluate seriously delinquent youngsters and identify pathology, which can be treated as needed. In all these endeavors, it is important that the availability of follow-up services be assured so that the diagnostic services do not become simply a form of labeling.

In state hospitals, youngsters transferred from correctional facilities are often treated in a discriminatory fashion. State mental health facilities should develop the expertise to deal with seriously disturbed offenders with good clinical acumen and to provide them with the full range of necessary services. In addition, cooperative arrangements need to be developed between correctional facilities and mental health facilities.

In order for psychiatrists to participate in the work of the juvenile justice system, modification of the core curricula of training programs will be needed. At the least, all programs should deal with normal development and psychopathology of children and adolescents. Furthermore, unless there are good role models and good working programs in the juvenile justice system, trainees will not find these areas appealing, since trainees learn by exposure and successful engagement in such programs.

Not every training program needs to provide direct work in court and correctional settings. However, psychiatric residents must learn good clinical skills and obtain appropriate training in interdisciplinary work. They need to learn the principles of consultation and liaison, including the means of communicating across disciplines to judges and lay people. They also need some grounding in basic forensics. In addition, they need to develop approaches to dealing with multidisciplinary problems, which may include health and educational problems as well as psychiatric issues. Furthermore, clinicians need to be able to distinguish cultural and psychopathological problems. They need to overcome their professional inadequacies and inexperience so that they can approach a juvenile murderer as confidently as they approach a disorganized psychotic individual. They need to understand more about family dynamics, organic factors that lead to personality and psychiatric disorders, and the role of environment and constitutional variables in creating psychopathology. They may have to broaden their approach to treatment programs to think in terms of offering psychiatric interventions in conjunction with educational and correctional approaches. They need to reorient themselves so that they can think of antisocial behavior as possibly being a manifestation of psychiatric disturbance.

Psychiatry programs need to become reinvolved with such issues as substance abuse and alcohol abuse; treating them as subspecialties denies many patients the opportunity for the full range of diagnostic and treatment approaches available. Psychiatrists need to relearn triage, i.e., how to identify what is psychiatric and what is the realm of other disciplines. The organization of training programs may need to bring universities more closely into work with correctional programs. The mutual enrichment derived by state hospitals and universities that work hand in hand can also result from collaboration between universities and correctional institutions. A specific training program in juvenile forensic psychiatry would include the following:

1. The history of society's efforts to deal with juvenile delinquents, including the development of the juvenile court and its subsequent evolution.
2. Legislative and judicial developments in the juvenile justice area.
3. Theories of delinquency and its causation from sociological, psychological, and biological perspectives.
4. Psychoanalytic theory and its contributions to the understanding of antisocial behavior.
5. The organization and operation of the juvenile court: the principal participants, from intake to adjudication and disposition.
6. Juvenile delinquents, status offenders, neglect and abuse cases, custody matters.
7. Comprehensive biopsychosocial evaluation of the child and his or her family.
8. Assessing competence and dangerousness.
9. Psychopathological perspectives, especially of psychotic, men-

tally retarded, severely depressed, suicidal, violent, and sexually aggressive offenders.

10. Psychodynamics of juvenile offenders' families.
11. Dispositional alternatives: diversion, protection, or placement; the welfare, correctional, or mental health system.
12. Rehabilitative versus punitive models.
13. Treatment issues, including modalities in use and their effectiveness.
14. Educational/vocational interventions and their goals.
15. Outcome studies.
16. Problems of postdisposition follow-up.
17. Writing reports to the court.
18. Testifying before the court: the psychiatrist as expert witness.
19. Coordinating efforts with probation, social services, legal aid, and other community agencies.
20. Teaching the relevant elements of normal child development and psychopathology to persons outside the mental health field and explaining psychiatric perspectives.

Research in the field of juvenile delinquency has come primarily from the social sciences. Clinical research is difficult enough with any patient population. The clinical perspective of a psychiatrist can inform the research team about the questions and variables that can help separate juvenile offenders into subpopulations with specific disorders and handicaps.

Research is needed regarding precursors of delinquent behavior, such as child abuse, head trauma, emergency room visits, and other variables beyond those which are sociocultural. Other areas for research are family dynamics and psychodynamics and identification of the clinical syndromes that are subsumed under delinquency. There is also a need for outcome studies for particular populations of delinquents, rather than the global studies currently being considered. There is a need to look at outcomes other than recidivism to measure the effectiveness of correctional programs and treatment programs. Cooperative research programs across institutions may need to be established in order to obtain large enough populations to achieve statistical significance.

Public advocacy is another role for psychiatrists in the area of juvenile delinquency. Legislators and laypersons need to know that frequently the distinction between those who enter the juvenile justice system and those who enter the mental health system has more to do with socioeconomic status and race than with the nature of their psychiatric disorders. We need to make clear that antisocial behavior may be an indicator of a significant underlying psychiatric disorder. The public needs to be informed that it is not sufficient simply to remove violent delinquents from the community, that it is necessary to make careful diagnostic assessments of this population and to identify and meet their treatment needs, in ways consistent with the need to protect society.

As a profession we need to be able to distinguish between interventions intended to protect the public and interventions intended to correct youngsters with disordered behavior and to assist families. We need to be able to obtain and protect funds for needed research. Above all, we need to be able to reaffirm our position that the relationship between behavior and psychopathology is the province of the psychiatrist, as well as other clinicians.

As stated earlier, there has been a history of sporadic involvement by APA and psychiatry in general in the field of juvenile delinquency. Juvenile delinquency, however, is not a transient problem, and the psychiatric aspects of this problem have always been present and will persist. Psychiatric involvement may be even more relevant at present than it has been in the past, since the pendulum seems to be swinging from rejection of the rehabilitative and treatment model in corrections to recognition of the need for more mental health clinical input. Members of the juvenile justice system are reaching out to mental health professionals. Other psychiatric organizations are turning to APA for leadership in this area and not delegation of the mental health presence in the field to other disciplines. As practice patterns change there will be increasing opportunities for psychiatrists to participate with this population, and many more positions will be available in the future.

APA has a commitment to tend to the mentally ill in underserved populations, and those in the juvenile justice system are among the most disadvantaged and hardest to treat. Such youngsters and their families need comprehensive psychiatric evaluations and treatment, and our profession needs to see them as part of our responsibility.

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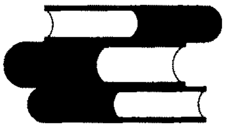

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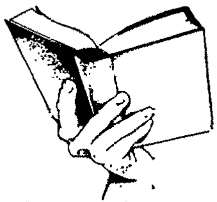

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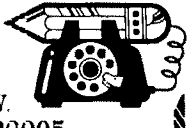

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March 22–24, annual meeting, Association for Child Psychoanalysis, St. Louis. Contact: Charles A. Mangham, M.D., President, P.O. Box 5935, Washington, DC 20016; 202-363-7849.

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April 3–5, 2nd International Congress on Emergency Psychiatry, Amsterdam. Contact: 2nd International Congress on Emergency Psychiatry, c/o Leids Congres Bureau, P.O. Box 16065, 2301 GB Leiden, The Netherlands; 31-71-275299.

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April 10–13, international conference, "Changing Mental Health Care in the Cities of Europe," Amsterdam. Contact: Congress Secretariat, QLT/CONGREX, Keizersgracht 782, 1017 EC Amsterdam, The Netherlands; 31-0-20-26-13-72.

April 11–14, annual meeting, American College of Physicians, New Orleans. Contact: John Ball, M.D., J.D., Executive Vice-President, Sixth Street at Race, Philadelphia, PA 19106; 215-351-2400.

April 15–19, annual meeting, American Society of Clinical Hypnosis, St. Louis. Contact: William F. Hoffmann, Jr., Executive Vice-President, 2250 East Devon Avenue, Suite 336, Des Plaines, IL 60018; 708-297-3317.

April 17–19, international symposium, "Eating Disorders," International Society for Adolescent Psychiatry in Association With the Eating Disorders Section of the World Psychiatric Association, Paris. Contact: Herman D. Staples, M.D., IACAPAP Coordinator for North America, 24 Green Valley Road, Wallingford, PA 19086.

April 17–21, annual meeting, American Association of Suicidology, Boston. Contact: Julie Perlman, M.S.W., Executive Officer, 2459 South Ash, Denver, CO 80222; 303-692-0985.

April 18–20, annual meeting, Society for Research in Child Development, Seattle. Contact: John W. Hagen, Executive Officer, 300 North Ingalls Boulevard, Ann Arbor, MI 48109-0406; 313-764-2443.

April 18–21, annual meeting, National Council on Alcoholism and Drug Dependence, Boston. Contact: Hamilton Beazley, President, 12 West 21st Street, 8th Floor, New York, NY 10010; 212-206-6770.

April 18–21, Ninth Annual Symposium in Forensic Psychiatry, American College of Forensic Psychiatry, Newport Beach, Calif. Contact: Ed Miller, Executive Director, 26701 Quail Creek, Suite 295, Laguna Hills, CA 92656; 714-831-0236.

April 21–24, annual meeting, American Association for Counseling and Development, Reno, Nev. Contact: William W. Hunter, Acting Executive Director, 5999 Stevenson Avenue, Alexandria, VA 22304; 703-823-9800.

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April 30–May 5, annual meeting, American Association of Sex Educators, Counselors and Therapists, St. Louis. Contact: David G. Lister, Executive Director, 435 North Michigan Avenue, Suite 1717, Chicago, IL 60611; 312-644-0828.

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By July 5 the agranulocytosis had reversed completely, and Michael was discharged from the medical unit and admitted to a psychiatric ward. Today Michael is receiving another antipsychotic agent. He remains symptomatic, but thanks to the special safety precautions initiated by CPMS, his life was saved.

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WARNINGS

General

BECAUSE OF THE SIGNIFICANT RISK OF AGRANULOCYTOSIS, A POTENTIALLY LIFE-THREATENING ADVERSE EVENT (SEE BELOW), CLOZARIL SHOULD BE RESERVED FOR USE IN THE TREATMENT OF SEVERELY ILL SCHIZOPHRENIC PATIENTS WHO FAIL TO SHOW AN ACCEPTABLE RESPONSE TO ADEQUATE COURSES OF STANDARD ANTIPSYCHOTIC DRUG TREATMENT, EITHER BECAUSE OF INSUFFICIENT EFFECTIVENESS OR THE INABILITY TO ACHIEVE AN EFFECTIVE DOSE DUE TO INTOLERABLE ADVERSE EFFECTS FROM THOSE DRUGS. CONSEQUENTLY, BEFORE INITIATING TREATMENT WITH CLOZARIL, IT IS STRONGLY RECOMMENDED THAT A PATIENT BE GIVEN AT LEAST TWO TRIALS, EACH WITH A DIFFERENT STANDARD ANTIPSYCHOTIC DRUG PRODUCT, AT AN ADEQUATE DOSE AND FOR AN ADEQUATE DURATION.

PATIENTS WHO ARE BEING TREATED WITH CLOZARIL MUST HAVE A BASELINE WHITE BLOOD CELL (WBC) AND DIFFERENTIAL COUNT BEFORE INITIATION OF TREATMENT, AND A WBC COUNT EVERY WEEK THROUGHOUT TREATMENT, AND FOR FOUR WEEKS AFTER THE DISCONTINUATION OF CLOZARIL.

CLOZARIL IS AVAILABLE ONLY THROUGH THE CLOZARIL PATIENT MANAGEMENT SYSTEM^{SM} (CPMS^{SM}).

Agranulocytosis

Agranulocytosis, defined as a granulocyte count (polys + bands) of less than 500 per mm^3, has been estimated to occur in association with CLOZARIL use at a cumulative incidence at one year of approximately 1.3%, based on the occurrence of 15 U.S. cases out of 1743 patients exposed to CLOZARIL during its clinical testing prior to domestic marketing. All of these cases occurred at a time when the need for close monitoring of WBC counts was already recognized. This reaction could prove fatal if not detected early and therapy interrupted. While no fatalities have been associated with the U.S. agranulocytosis cases, and all cases have recovered fully, the U.S. sample is too small to reliably estimate the case fatality rate. Of the 112 cases of agranulocytosis reported worldwide in association with CLOZARIL use as of December 31, 1986, 35% were fatal. However, few of these deaths occurred since 1977, at which time the knowledge of CLOZARIL-induced agranulocytosis became more widespread, and close monitoring of WBC counts more widely practiced. Nevertheless, it is unknown at present what the case fatality rate will be for CLOZARIL-induced agranulocytosis, despite strict adherence to the recommendation for weekly monitoring of WBC counts.

Treatment should not be initiated if the WBC count is less than 3500 per mm^3, or if the patient has a history of a myeloproliferative disorder, or previous CLOZARIL-induced agranulocytosis or granulocytopenia. Patients should be advised to report immediately the appearance of lethargy, weakness, fever, sore throat or any other signs of infection. If, after the initiation of treatment, the total WBC count has dropped below 3500 per mm^3 or it has dropped by a substantial amount from baseline, even if the count is above 3500 per mm^3, or if immature forms are present, a repeat WBC count and a differential count should be done. If subsequent WBC counts and the differential count reveal a total WBC count between 3000 and 3500 per mm^3 and a granulocyte count above 1500 per mm^3, twice weekly WBC counts and differential counts should be performed.

If the total WBC count falls below 3000 per mm^3 or the granulocyte count below 1500 per mm^3, CLOZARIL therapy should be interrupted and patients should be carefully monitored for flu-like symptoms or other symptoms suggestive of infection. CLOZARIL therapy may be resumed if no symptoms of infection develop, and if the total WBC count returns to levels above 3000 per mm^3 and the granulocyte count returns to levels above 1500 per mm^3. However, in this event, twice-weekly WBC counts and differential counts should continue until total WBC counts return to levels above 3500 per mm^3.

If the total WBC count falls below 2000 per mm^3 or the granulocyte count falls below 1000 per mm^3, bone marrow aspiration should be considered to ascertain granulopoietic status. Protective isolation with close observation may be indicated if granulopoiesis is determined to be deficient. Should evidence of infection develop, the patient should have appropriate cultures performed and an appropriate antibiotic regimen instituted.

Patients whose total WBC counts fall below 2000 per mm^3, or granulocyte counts below 1000 per mm^3 during CLOZARIL therapy should *not* be re-challenged with CLOZARIL. Patients discontinued from CLOZARIL therapy due to significant WBC suppression have been found to develop agranulocytosis upon re-challenge, often with a shorter latency on re-exposure. To reduce the chances of re-challenge occurring in patients who have experienced significant bone marrow suppression during CLOZARIL therapy, a single, national master file will be maintained confidentially within the CPMS (Clozaril Patient Management System).

Except for evidence of significant bone marrow suppression during initial CLOZARIL therapy, there are no established risk factors, based on worldwide experience, for the development of agranulocytosis in association with CLOZARIL use. However, a disproportionate number of the U.S. cases of agranulocytosis occurred in patients of Jewish background compared to the overall proportion of such patients exposed during the domestic development of CLOZARIL. Most of the U.S. cases occurred within 4-10 weeks of exposure, but neither dose nor duration is a reliable predictor of this problem. No patient characteristics have been clearly linked to the development of agranulocytosis in association with CLOZARIL use, but agranulocytosis associated with other antipsychotic drugs has been reported to occur with a greater frequency in women, the elderly and in patients who are cachectic or have serious underlying medical illness; such patients may also be at particular risk with CLOZARIL.

To reduce the risk of agranulocytosis developing undetected, CLOZARIL will be dispensed only within the Clozaril Patient Management System.

Seizures

Seizure has been estimated to occur in association with CLOZARIL use at a cumulative incidence at one year of approximately 5%, based on the occurrence of one or more seizures in 61 of 1743 patients exposed to CLOZARIL during its clinical testing prior to domestic marketing (i.e., a crude rate of 3.5%). Dose appears to be an important predictor of seizure, with a greater likelihood of seizure at the higher CLOZARIL doses used.

Caution should be used in administering CLOZARIL to patients having a history of seizures or other predisposing factors. Because of the substantial risk of seizure associated with CLOZARIL use, patients should be advised not to engage in any activity where sudden loss of consciousness could cause serious risk to themselves or others, e.g., the operation of complex machinery, driving an automobile, swimming, climbing, etc.

Adverse Cardiovascular Effects

Orthostatic hypotension can occur with CLOZARIL treatment, especially during initial titration in association with rapid dose escalation, and may represent a continuing risk in some patients. Tachycardia, which may be sustained, has also been observed in approximately 25% of patients taking CLOZARIL, with patients having an average increase in pulse rate of 10-15 bpm. The sustained tachycardia is not simply a reflex response to hypotension, and is present in all positions monitored. Either tachycardia or hypotension may pose a serious risk for an individual with compromised cardiovascular function. A minority of CLOZARIL-treated patients experience ECG repolarization changes similar to those seen with other antipsychotic drugs, including S-T segment depression and flattening or inversion of T waves, which all normalize after discontinuation of CLOZARIL. The clinical significance of these changes is unclear. However, in clinical trials with CLOZARIL, several patients experienced significant cardiac events, including ischemic changes, myocardial infarction, nonfatal arrhythmias and sudden unexplained death. Causality assessment was difficult in many of these cases because of serious preexisting cardiac disease and plausible alternative causes. Rare instances of sudden, unexplained death have been reported in psychiatric patients, with or without associated antipsychotic drug treatment, and the relationship of these events to antipsychotic drug use is unknown. CLOZARIL should be used with caution in patients with known cardiovascular disease, and the recommendation for gradual titration of dose should be carefully observed.

Neuroleptic Malignant Syndrome

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). No cases of NMS have been attributed to CLOZARIL alone. However, there have been several reported cases of NMS in patients treated concomitantly with lithium or other CNS-active agents.

Tardive Dyskinesia

A syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of treatment, which patients are likely to develop the syndrome.

There are several reasons for predicting that CLOZARIL may be different from other antipsychotic drugs in its potential for inducing tardive dyskinesia, including the preclinical finding that it has a relatively weak dopamine blocking effect and the clinical finding of a virtual absence of certain acute extrapyramidal symptoms, e.g., dystonia. In addition, there have been no confirmed cases of tardive dyskinesia developing in association with CLOZARIL use. Nevertheless, it cannot yet be concluded, without more extended experience, that CLOZARIL is incapable of inducing this syndrome.

PRECAUTIONS

Because of the significant risk of agranulocytosis and seizure, both of which present a continuing risk over time, the extended treatment of patients failing to show an acceptable level of clinical response should ordinarily be avoided. In addition, the need for continuing treatment in patients exhibiting beneficial clinical responses should be periodically re-evaluated. During CLOZARIL therapy, patients may experience transient temperature elevations above 100.4°F (38°C), with the peak incidence within the first three weeks of treatment. While this fever is generally benign and self-limiting, it may necessitate discontinuing patients from treatment. On occasion, there may be an associated increase or decrease in WBC count. Patients with fever should be carefully evaluated to rule out the possibility of an underlying infectious process or the development of agranulocytosis. In the presence of high fever, the possibility of neuroleptic malignant syndrome (NMS) must be considered. CLOZARIL has very potent anticholinergic effects, and great care should be exercised in using this drug in the presence of prostatic enlargement or narrow angle glaucoma. Because of initial sedation, CLOZARIL may impair mental and/or physical abilities, especially during the first few days of therapy. The recommendations for gradual dose escalation should be carefully adhered to, and patients cautioned about activities requiring alertness. Clinical experience with CLOZARIL in patients with concomitant systemic diseases is limited. Nevertheless, caution is advisable in using CLOZARIL in patients with hepatic, renal or cardiac disease.

Information for Patients

Patients who are to receive CLOZARIL should be warned about the significant risk of developing agranulocytosis. They should be informed that weekly blood tests are required to monitor for the occurrence of agranulocytosis, and that CLOZARIL tablets will be made available only through a special program designed to ensure the required blood monitoring. Patients should be advised to report immediately the appearance of lethargy, weakness, fever, sore throat, malaise, mucous membrane ulceration or other possible signs of infection. Particular attention should be paid to any flu-like complaints or other symptoms that might suggest infection. Patients should be informed of the significant risk of seizure during CLOZARIL treatment, and they should be advised to avoid driving and any other potentially hazardous activity while taking CLOZARIL. Patients should be advised of the risk of orthostatic hypotension, especially during the period of initial dose titration. Patients should notify their physician if they are taking, or plan to take, any prescription or over-the-counter drugs or alcohol. Patients should notify their physician if they become pregnant or intend to become pregnant during therapy. Patients should not breast feed an infant if they are taking CLOZARIL.

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TABLETS

Drug Interactions

The risks of using CLOZARIL in combination with other drugs have not been systematically evaluated. The mechanism of CLOZARIL-induced agranulocytosis is unknown; nonetheless, the possibility that causative factors may interact synergistically to increase the risk and/or severity of bone marrow suppression warrants consideration. Therefore, CLOZARIL should not be used with other agents having a well-known potential to suppress bone marrow function. Given the primary CNS effects of CLOZARIL, caution is advised in using it concomitantly with other CNS-active drugs. Because CLOZARIL is highly bound to serum protein, the administration of CLOZARIL to a patient taking another drug which is highly bound to protein (e.g., warfarin, digoxin) may cause an increase in plasma concentrations of these drugs. potentially resulting in adverse effects. Conversely, adverse effects may result from displacement of protein-bound CLOZARIL by other highly bound drugs.

CLOZARIL may also potentiate the hypotensive effects of antihypertensive drugs and the anticholinergic effects of atropine-type drugs. The administration of epinephrine should be avoided in the treatment of drug-induced hypotension because of a possible reverse epinephrine effect.

Pregnancy Category B

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, and in view of the desirability of keeping the administration of all drugs to a minimum during pregnancy, this drug should be used only if clearly needed.

ADVERSE REACTIONS

Adverse events observed in association with the use of CLOZARIL in clinical trials at an incidence of 5% or greater were: central nervous system complaints, including drowsiness/sedation, dizziness/vertigo, headache and tremor; autonomic nervous system complaints, including salivation, sweating, dry mouth and visual disturbances; cardiovascular findings, including tachycardia, hypotension and syncope; and gastrointestinal complaints, including constipation and nausea; and fever. Complaints of drowsiness/sedation tend to subside with continued therapy or dose reduction. Salivation may be profuse, especially during sleep, but may be diminished with dose reduction.

DOSAGE AND ADMINISTRATION

Initial Treatment

It is recommended that treatment with CLOZARIL begin at 25 mg once or twice daily, and then be continued with daily dosage increments of 25 to 50 mg/day, if well-tolerated, to achieve a target dose of 300 to 450 mg/day by the end of two weeks. Subsequent dosage increments should be made no more than once- or twice-weekly, in increments not to exceed 100 mg. Cautious titration and a divided dosage schedule are necessary to minimize the risks of hypotension, seizure, and sedation.

Therapeutic Dose Adjustment

Daily dosing should continue on a divided basis as an effective and tolerable dose level is sought. While many patients may respond adequately at doses between 300-600 mg/day, it may be necessary to raise the dose to the 600-900 mg/day range to obtain an acceptable response. [Note: In the multicenter study providing the primary support for the superiority of CLOZARIL in treatment resistant patients, the mean and median CLOZARIL doses were both approximately 600 mg/day.]

Because of the possibility of increased adverse reactions at higher doses, particularly seizures, patients should ordinarily be given adequate time to respond to a given dose level before escalation to a higher dose is contemplated.

Dosing should not exceed 900 mg/day.

Discontinuation of Treatment

In the event of planned termination of CLOZARIL therapy, gradual reduction in dose is recommended over a 1 to 2 week period. However, should a patient's medical condition require abrupt discontinuation (e.g., leukopenia), the patient should be carefully observed for the recurrence of psychotic symptoms.

CLOZARIL is available only through the Clozaril Patient Management System, a program that combines white blood cell testing, patient monitoring, pharmacy, and drug distribution services, all linked to compliance with required safety monitoring.

To prescribe CLOZARIL call 1-800-237-CPMS (2767) or mail in a completed CPMS Enrollment Form.

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Candidates must:

- possess the M.D., degree in psychiatry or the M.R.C.P.I. in psychiatry or membership of the Royal College of Psychiatrists or the Diploma in Psychological Medicines awarded before February 1972 or a professional qualification at least equivalent to one of these; and
- have at least seven years satisfactory experience (after becoming entitled to full registration) in the practice of the medical profession including not less than five years satisfactory experience in psychiatry of which not less than three years was in mental handicap psychiatry.

Application forms and further information available from John Pepper, Human Resources Manager, Provincial Administration, Stillorgan, Co. Dublin, Eire. Tel.: Dublin 831201.

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HEAD, DEPARTMENT OF PSYCHIATRY

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Dean, Faculty of Medicine
Room 317, Instructional Resources Centre
University of British Columbia
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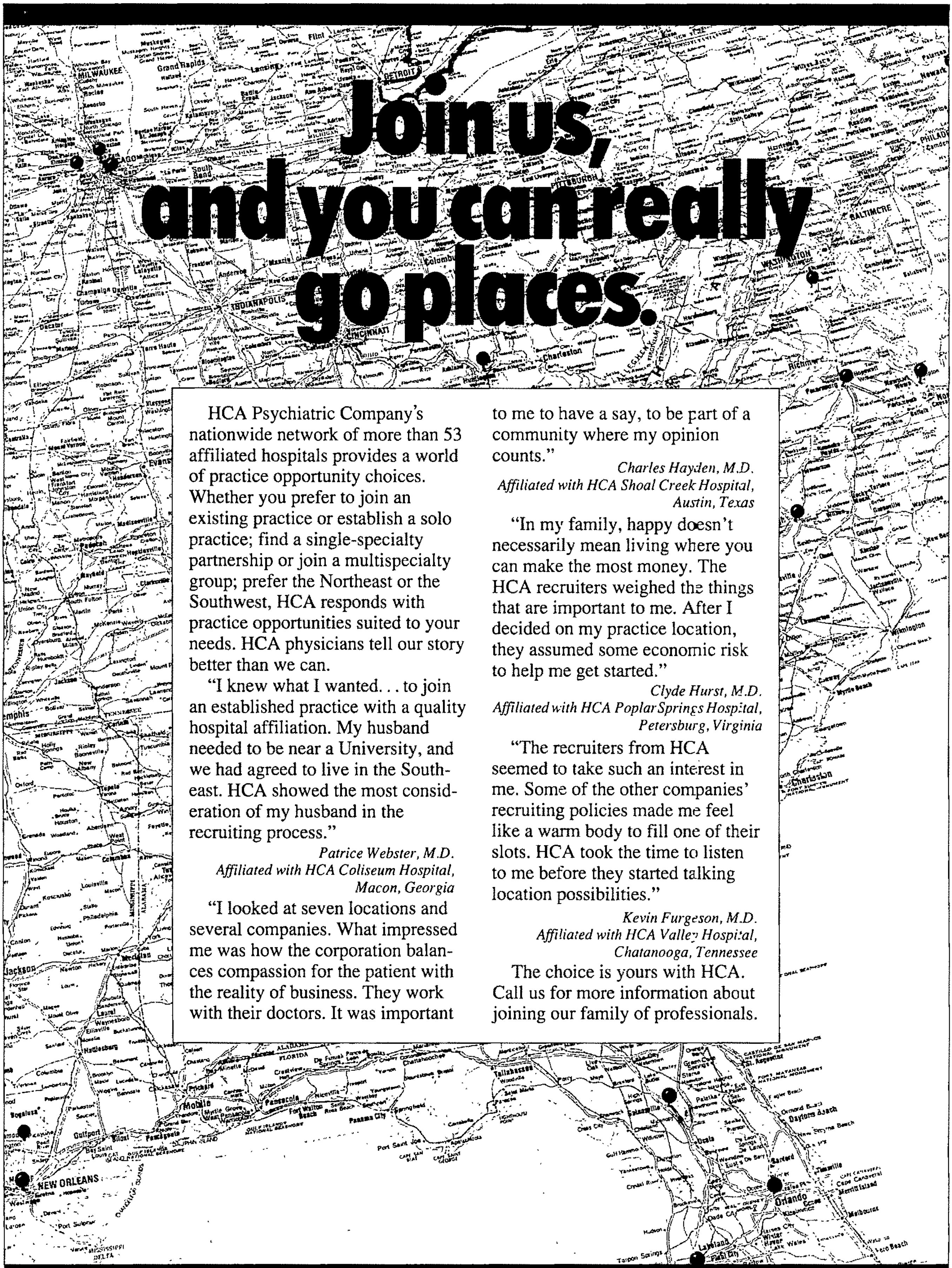
Vancouver, B.C. V6T 1W5



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(*other than a primary degree).

(b) At least seven years satisfactory experience (after becoming entitled to full registration) in the practice of the medical profession, including not less than five years satisfactory experience in psychiatry of which not less than three years was in child psychiatry.

Application forms and further information available from John Pepper, Human Resource Manager, Provincial Administration, Stillorgan, Co. Dublin Eire. Tel.: Dublin 831201

Closing Date: 7th December, 1990.

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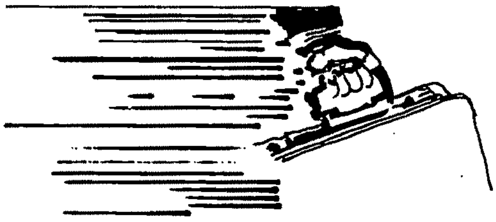

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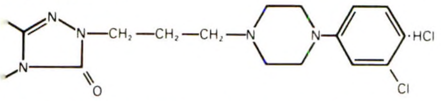

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ONS AND USAGE

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NDICATIONS

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TIONS

sibility of suicide in seriously depressed patients is inherent in the illness and may ntil significant remission occurs. Therefore, prescriptions should be written for the number of tablets consistent with good patient management.

sion, including orthostatic hypotension and syncope, has been reported to occur in receiving DESYREL. Concomitant administration of antihypertensive therapy with may require a reduction in the dose of the antihypertensive drug.

known about the interaction between DESYREL and general anesthetics; therefore, elective surgery, DESYREL should be discontinued for as long as clinically feasible.

ll antidepressants, the use of DESYREL should be based on the consideration of the that the expected benefits of therapy outweigh potential risk factors.

ion for Patients:
priapism has been reported to occur in patients receiving DESYREL, patients with d or inappropriate penile erection should immediately discontinue the drug and consult physician (see WARNINGS).

essants may impair the mental and/or physical ability required for the performance of ly hazardous tasks, such as operating an automobile or machinery; the patient should oned accordingly.

may enhance the response to alcohol, barbiturates, and other CNS depressants.

L should be given shortly after a meal or light snack. Within any individual patient, total sorption may be up to 20% higher when the drug is taken with food rather than on an tomach. The risk of dizziness/lightheadedness may increase under fasting conditions.

Laboratory Tests:
Occasional low white blood cell and neutrophil counts have been noted in patients receiving DESYREL® (trazodone hydrochloride). These were not considered clinically significant and did not necessitate discontinuation of the drug; however, the drug should be discontinued in any patient whose white blood cell count or absolute neutrophil count falls below normal levels. White blood cell and differential counts are recommended for patients who develop fever and sore throat (or other signs of infection) during therapy.

Drug Interactions:
Increased serum digoxin or phenytoin levels have been reported to occur in patients receiving DESYREL concurrently with either of those two drugs.

It is not known whether interactions will occur between monoamine oxidase (MAO) inhibitors and DESYREL. Due to the absence of clinical experience, if MAO inhibitors are discontinued shortly before or are to be given concomitantly with DESYREL, therapy should be initiated cautiously with gradual increase in dosage until optimum response is achieved.

Therapeutic Interactions:
Concurrent administration with electroshock therapy should be avoided because of the absence of experience in this area.

There have been reports of increased and decreased prothrombin time occurring in Coumadinized patients who take DESYREL.

Carcinogenesis, Mutagenesis, Impairment of Fertility:
No drug- or dose-related occurrence of carcinogenesis was evident in rats receiving DESYREL in daily oral doses up to 300 mg/kg for 18 months.

Pregnancy Category C:
DESYREL has been shown to cause increased fetal resorption and other adverse effects on the fetus in two studies using the rat when given at dose levels approximately 30-50 times the proposed maximum human dose. There was also an increase in congenital anomalies in one of three rabbit studies at approximately 15-50 times the maximum human dose. There are no adequate and well-controlled studies in pregnant women. DESYREL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers:
DESYREL and/or its metabolites have been found in the milk of lactating rats, suggesting that the drug may be secreted in human milk. Caution should be exercised when DESYREL is administered to a nursing woman.

Pediatric Use:
Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS

Because the frequency of adverse drug effects is affected by diverse factors (e.g., drug dose, method of detection, physician judgment, disease under treatment, etc.) a single meaningful estimate of adverse event incidence is difficult to obtain. This problem is illustrated by the variation in adverse event incidence observed and reported from the inpatients and outpatients treated with DESYREL. It is impossible to determine precisely what accounts for the differences observed.

Clinical Trial Reports:
The table below is presented solely to indicate the relative frequency of adverse events reported in representative controlled clinical studies conducted to evaluate the safety and efficacy of DESYREL.

The figures cited cannot be used to predict precisely the incidence of untoward events in the course of usual medical practice where patient characteristics and other factors often differ from those which prevailed in the clinical trials. These incidence figures, also, cannot be compared with those obtained from other clinical studies involving related drug products and placebo as each group of drug trials is conducted under a different set of conditions.

	Treatment-Emergent Symptom Incidence			
	Inpts.		Outpts.	
	D	P	D	P
Number of Patients	142	95	157	158
% of Patients Reporting				
Allergic				
Skin Condition/Edema	2.8	1.1	7.0	1.3
Autonomic				
Blurred Vision	6.3	4.2	14.7	3.8
Constipation	7.0	4.2	7.6	5.7
Dry Mouth	14.8	8.4	33.8	20.3
Cardiovascular				
Hypertension	2.1	1.1	1.3	*
Hypotension	7.0	1.1	3.8	0.0
Shortness of Breath	*	1.1	1.3	0.0
Syncope	2.8	2.1	4.5	1.3
Tachycardia/Palpitations	0.0	0.0	7.0	7.0
CNS				
Anger/Hostility	3.5	6.3	1.3	2.5
Confusion	4.9	0.0	5.7	7.6
Decreased Concentration	2.8	2.1	1.3	0.0
Disorientation	2.1	0.0	*	0.0
Dizziness/Lightheadedness	19.7	5.3	28.0	15.2
Drowsiness	23.9	6.3	40.8	19.6
Excitement	1.4	1.1	5.1	5.7
Fatigue	11.3	4.2	5.7	2.5
Headache	9.9	5.3	19.8	15.8
Insomnia	9.9	10.5	6.4	12.0
Impaired Memory	1.4	0.0	*	*
Nervousness	14.8	10.5	6.4	8.2
Gastrointestinal				
Abdominal/Gastric Disorder	3.5	4.2	5.7	4.4
Bad Taste in Mouth	1.4	0.0	0.0	0.0
Diarrhea	0.0	1.1	4.5	1.9
Nausea/Vomiting	9.9	1.1	12.7	9.5
Musculoskeletal				
Musculoskeletal Aches/Pains	5.6	3.2	5.1	2.5
Neurological				
Incoordination	4.9	0.0	1.9	0.0
Paresthesia	1.4	0.0	0.0	*
Tremors	2.8	1.1	5.1	3.8
Sexual Function				
Decreased Libido	*	1.1	1.3	*
Other				
Decreased Appetite	3.5	5.3	0.0	*
Eyes Red/Tired/Itching	2.8	0.0	0.0	0.0
Head Full-Heavy	2.8	0.0	0.0	0.0
Malaise	2.8	0.0	0.0	0.0
Nasal/Sinus Congestion	2.8	0.0	5.7	3.2
Nightmares/Vivid Dreams	*	1.1	5.1	5.7
Sweating/Clamminess	1.4	1.1	*	*
Tinnitus	1.4	0.0	0.0	*
Weight Gain	1.4	0.0	4.5	1.9
Weight Loss	*	3.2	5.7	2.5

* Incidence less than 1%.

D = DESYREL P = Placebo

Occasional sinus bradycardia has occurred in long-term studies.

In addition to the relatively common (i.e., greater than 1%) untoward events enumerated above, the following adverse events have been reported to occur in association with the us DESYREL® (trazodone hydrochloride) in the controlled clinical studies: akathisia, allergic re tion, anemia, chest pain, delayed urine flow, early menses, flatulence, hallucinations/delusio hematuria, hypersalivation, hypomania, impaired speech, impotence, increased appetite, creased libido, increased urinary frequency, missed periods, muscle twitches, numbness, retrograde ejaculation.

Postintroduction Reports:
Although the following adverse reactions have been reported in DESYREL users, the ca association has neither been confirmed nor refuted.

Voluntary reports received since market introduction include the following: agitation, alope apnea, ataxia, breast enlargement or engorgement, diplopia, edema, extrapyramidal sy toms, grand mal seizures, hallucinations, hemolytic anemia, hyperbilirubinemia, leukonycl jaundice, lactation, liver enzyme alterations, methemoglobinemia, nausea/vomiting (most quently), paresthesia, priapism (See WARNINGS and PRECAUTIONS, Information for Patie some patients have required surgical intervention), pruritis, psychosis, rash, stupor, inap priate ADH syndrome, tardive dyskinesia, unexplained death, urinary incontinence, urin retention, urticaria, vasodilation, vertigo and weakness.

Cardiovascular system effects which have been reported include the following: conduc block, orthostatic hypotension and syncope, palpitations, bradycardia, atrial fibrillation, m cardial infarction, cardiac arrest, arrhythmia, and ventricular ectopic activity, including vent ular tachycardia (see WARNINGS).

OVERDOSE

Animal Oral LD_{50}

The oral LD_{50} of the drug is 610 mg/kg in mice, 486 mg/kg in rats, and 560 mg/kg in rabb

Signs and Symptoms:
Death from overdose has occurred in patients ingesting DESYREL (trazodone hydrochlori and other drugs concurrently (namely, alcohol; alcohol + chloral hydrate + diazepam; a barbital; chlordiazepoxide; or meprobamate).

The most severe reactions reported to have occurred with overdose of DESYREL alone h been priapism, respiratory arrest, seizures, and EKG changes. The reactions reported m frequently have been drowsiness and vomiting. Overdosage may cause an increase in incide or severity of any of the reported adverse reactions (see ADVERSE REACTIONS).

Treatment:
There is no specific antidote for DESYREL. Treatment should be symptomatic and supporti the case of hypotension or excessive sedation. Any patient suspected of having taken overdose should have the stomach emptied by gastric lavage. Forced diuresis may be usefu facilitating elimination of the drug.

DOSAGE AND ADMINISTRATION

The dosage should be initiated at a low level and increased gradually, noting the clin response and any evidence of intolerance. Occurrence of drowsiness may require the admi tration of a major portion of the daily dose at bedtime or a reduction of dosage. DESY should be taken shortly after a meal or light snack. Symptomatic relief may be seen during first week, with optimal antidepressant effects typically evident within two weeks. Twenty- percent of those who respond to DESYREL require more than two weeks (up to four weeks) drug administration.

Usual Adult Dosage:
An initial dose of 150 mg/day in divided doses is suggested. The dose may be increased by mg/day every three to four days. The maximum dose for outpatients usually should not exce 400 mg/day in divided doses. Inpatients (i.e., more severely depressed patients) may be gi up to but not in excess of 600 mg/day in divided doses.

Maintenance:
Dosage during prolonged maintenance therapy should be kept at the lowest effective le Once an adequate response has been achieved, dosage may be gradually reduced, w subsequent adjustment depending on therapeutic response.

Although there has been no systematic evaluation of the efficacy of DESYREL beyond weeks, it is generally recommended that a course of antidepressant drug treatment should continued for several months.

HOW SUPPLIED

DESYREL (trazodone hydrochloride)

Tablets, 50 mg — round, orange/scored, film-sealed (imprinted with DESYREL and MJ 7

NDC 0087-0775-41 Bottles of 100
NDC 0087-0775-43 Bottles of 1000
NDC 0087-0775-42 Cartons of 100 Unit Doses

Tablets, 100 mg — round, white/scored, film-sealed (imprinted with DESYREL and MJ 7

NDC 0087-0776-41 Bottles of 100
NDC 0087-0776-43 Bottles of 1000
NDC 0087-0776-42 Cartons of 100 Unit Doses

Tablets, 150 mg — orange, in the Dividose® tablet design (imprinted with MJ and 778 on fr "50," "50," "50" on reverse)

NDC 0087-0778-43 Bottles of 100
NDC 0087-0778-44 Bottles of 500

Tablets, 300 mg — yellow, in the Dividose® tablet design (imprinted with MJ and 796 on fr "100," "100," "100" on reverse)
NDC 0087-0796-41 Bottles of 100

U.S. Patent No. 4,215,104

Store at room temperature. Protect from temperatures above 104°F (40°C).

Dispense in tight, light-resistant container (USP).

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HELPS RELIEVE INSOMNIA SYMPTOMS ASSOCIATED WITH DEPRESSION *AND* TREATS THE DEPRESSION

Unique 300 mg and 150 mg Dividose tablets make daily dosing flexible and easy. Maximum dosage is 400 mg/d in divided doses for outpatients and 600 mg/d in divided doses for inpatients. Initial therapy is 150 mg/d of Desyrel Dividose in divided doses.

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THE AMERICAN JOURNAL OF PSYCHIATRY

Volume 147, Number 12 December 1990

In this issue:

The Déjà Vu Experience: Remembrance of Things Past?
By Herman N. Sno and Don H. Linszen

Official Journal of the American Psychiatric Association

Her anxiolytic
is working—
but she's alert,
functioning, and
at no risk of a
benzodiazepine
withdrawal
syndrome when
therapy ends.

BuSpar® (buspirone HCl)

References: 1. Rickels K, et al: Buspirone and diazepam in anxiety: A controlled study. *J Clin Psychiatry* 1982;43(12, Sec 2):81-86. **2.** Newton RE, et al: A review of the side effect profile of buspirone. *Am J Med* 1986;80(suppl 3B):17-21. **3.** Lucki I, et al: Differential effects of the anxiolytic drugs, diazepam and buspirone, on memory function. *Br J Clin Pharmacol* 1987;23:207-211. **4.** Lader M: Assessing the potential for buspirone dependence or abuse and effects of its withdrawal. *Am J Med* 1987;82(suppl 5A):20-26.

Contraindications: Hypersensitivity to buspirone hydrochloride.

Warnings: The administration of BuSpar to a patient taking a monoamine oxidase inhibitor (MAOI) may pose a hazard. Since blood pressure has become elevated when BuSpar was administered concomitantly with an MAOI, such concomitant use is not recommended. BuSpar should not be employed in lieu of appropriate antipsychotic treatment.

Precautions: *General*—*Interference with cognitive and motor performance:* Although buspirone is less sedating than other anxiolytics and does not produce significant functional impairment, its CNS effects in a given patient may not be predictable; therefore, patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that buspirone does not affect them adversely. Although buspirone has not been shown to increase alcohol-induced impairment in motor and mental performance, it is prudent to avoid concomitant use with alcohol.

Potential for withdrawal reactions in sedative/hypnotic/anxiolytic drug dependent patients: Because buspirone will not block the withdrawal syndrome often seen with cessation of therapy with benzodiazepines and other common sedative/hypnotic drugs, before starting buspirone withdraw patients gradually from their prior treatment, especially those who used a CNS depressant chronically. Rebound or withdrawal symptoms may occur over varying time periods, depending in part on the type of drug and its elimination half-life. The withdrawal syndrome can appear as any combination of irritability, anxiety, agitation, insomnia, tremor, abdominal cramps, muscle cramps, vomiting, sweating, flu-like symptoms without fever, and occasionally, even as seizures.

Possible concerns related to buspirone's binding to dopamine receptors: Because buspirone can bind to central dopamine receptors, a question has been raised about its potential to cause acute and chronic changes in dopamine mediated neurological function (eg, dystonia, pseudoparkinsonism, akathisia, and tardive dyskinesia). Clinical experience in controlled trials has failed to identify any significant neuroleptic-like activity; however, a syndrome of restlessness, appearing shortly after initiation of treatment, has been reported; the syndrome may be due to increased central noradrenergic activity or may be attributable to dopaminergic effects (ie, represent akathisia).

***Information for Patients*—**Patients should be instructed to inform their physician about any medications, prescription or nonprescription, alcohol or drugs they are now taking or plan to take during treatment with buspirone; to inform their physician if they are pregnant, are planning to become pregnant, or become pregnant while taking buspirone; to inform their physician if they are breast feeding; and not to drive a car or operate potentially dangerous machinery until they experience how this medication affects them.

***Drug Interactions*—**Concomitant use with other CNS active drugs should be approached with caution (see **Warnings**). Concomitant use with trazodone may have caused 3- to 6-fold elevations on SGPT (ALT) in a few patients. Concomitant administration of BuSpar and haloperidol resulted in increased serum haloperidol concentrations in normal volunteers. The clinical significance is not clear. Buspirone does not displace tightly bound drugs like phenytoin, propranolol, and warfarin from serum proteins, but may displace less firmly bound drugs like digoxin. However, there was one report of prolonged prothrombin time when buspirone was given to a patient also treated with warfarin, phenytoin, phenobarbital, digoxin, and Synthroid.

***Carcinogenesis, Mutagenesis, Impairment of Fertility*—**No evidence of carcinogenic potential was observed in rats or mice; buspirone did not induce point mutations, nor was DNA damage observed; chromosomal aberrations or abnormalities did not occur.

***Pregnancy: Teratogenic Effects*—**Pregnancy Category B: Should be used during pregnancy only if clearly needed.

***Nursing Mothers*—**Administration to nursing women should be avoided if clinically possible.

***Pediatric Use*—**The safety and effectiveness have not been determined in individuals below 18 years of age.

***Use in the Elderly*—**No unusual, adverse, age-related phenomena have been identified in elderly patients receiving a total, modal daily dose of 15 mg.

***Use in Patients with Impaired Hepatic or Renal Function*—**Since buspirone is metabolized by the liver and excreted by the kidneys, it is not recommended in severe hepatic or renal impairment.

Adverse Reactions (See also Precautions): *Commonly Observed*—The more commonly observed untoward events, not seen at an equivalent incidence in placebo-treated patients, include dizziness, nausea, headache, nervousness, lightheadedness, and excitement.

***Associated with Discontinuation of Treatment*—**The more common events causing discontinuation in-

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...without significant cognitive[3] or functional impairment*

...without a benzodiazepine withdrawal syndrome on discontinuation[4]

Well tolerated

The more commonly observed untoward events associated with the use of BuSpar not seen at an equivalent incidence among placebo-treated patients include dizziness (12%), nausea (8%), headache (6%), nervousness (5%), lightheadedness (3%), and excitement (2%).

*Because the effects of BuSpar in any individual patient may not be predictable, patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that BuSpar treatment does not affect them adversely.

cluded: central nervous system disturbances (3.4%), primarily dizziness, insomnia, nervousness, drowsiness, lightheaded feeling; gastrointestinal disturbances (1.2%), primarily nausea; miscellaneous disturbances (1.1%), primarily headache and fatigue. In addition, 3.4% of patients had multiple complaints, none of which could be characterized as primary.

***Incidence in Controlled Clinical Trials*—**Adverse events reported by 1% or more of 477 patients who received buspirone in four-week, controlled trials: *Cardiovascular:* Tachycardia/palpitations 1%. *CNS:* Dizziness 12%, drowsiness 10%, nervousness 5%, insomnia 3%, lightheadedness 3%, decreased concentration 2%, excitement 2%, anger/hostility 2%, confusion 2%, depression 2%. *EENT:* Blurred vision 2%. *Gastrointestinal:* Nausea 8%, dry mouth 3%, abdominal/gastric distress 2%, diarrhea 2%, constipation 1%, vomiting 1%. *Musculoskeletal:* Musculoskeletal aches/pains 1%. *Neurological:* Numbness 2%, paresthesia 1%, incoordination 1%, tremor 1%. *Skin:* Skin rash 1%. *Miscellaneous:* Headache 6%, fatigue 4%, weakness 2%, sweating/clamminess 1%.

***Other Events Observed During the Entire Premarketing Evaluation*—**The relative frequency of all other undesirable events reasonably associated with the use of buspirone in approximately 3000 subjects who took multiple doses of the drug under well-controlled, open, and uncontrolled conditions is defined as follows: Frequent are those occurring in at least 1/100 patients; infrequent are those occurring in 1/100 to 1/1000 patients; and rare are those occurring in less than 1/1000 patients. *Cardiovascular*—frequent: non-specific chest pain; infrequent: syncope, hypotension, hypertension; rare: cerebrovascular accident, congestive heart failure, myocardial infarction, cardiomyopathy, bradycardia. *Central Nervous System*—frequent: dream disturbances; infrequent: depersonalization, dysphoria, noise intolerance, euphoria, akathisia, fearfulness, loss of interest, dissociative reaction, hallucinations, suicidal ideation, seizures; rare: feelings of claustrophobia, cold intolerance, stupor, slurred speech, psychosis. *EENT*—frequent: tinnitus, sore throat, nasal congestion; infrequent: redness and itching of the eyes, altered taste, altered smell, conjunctivitis; rare: inner ear abnormality, eye pain, photophobia, pressure on eyes. *Endocrine*—rare: galactorrhea, thyroid abnormality. *Gastrointestinal*—infrequent: flatulence, anorexia, increased appetite, salivation, irritable colon, rectal bleeding; rare: burning of the tongue. *Genitourinary*—infrequent: urinary frequency, urinary hesitancy, menstrual irregularity and spotting, dysuria; rare: amenorrhea, pelvic inflammatory disease, enuresis, nocturia. *Musculoskeletal*—infrequent: muscle cramps, muscle spasms, rigid/stiff muscles, arthralgias. *Neurological*—infrequent: involuntary movements, slowed reaction time; rare: muscle weakness. *Respiratory*—infrequent: hyperventilation, shortness of breath, chest congestion; rare: epistaxis. *Sexual Function*—infrequent: decreased or increased libido; rare: delayed ejaculation, impotence. *Skin*—infrequent: edema, pruritus, flushing, easy bruising, hair loss, dry skin, facial edema, blisters; rare: acne, thinning of nails. *Clinical Laboratory*—infrequent: increases in hepatic aminotransferases (SGOT, SGPT); rare: eosinophilia, leukopenia, thrombocytopenia. *Miscellaneous*—infrequent: weight gain, fever, roaring sensation in the head, weight loss, malaise; rare: alcohol abuse, bleeding disturbance, loss of voice, hiccoughs.

***Postintroduction Clinical Experience*—**Rare occurrences of allergic reactions, cogwheel rigidity, dystonic reactions, ecchymosis, emotional lability, tunnel vision, and urinary retention have been reported. Because of the uncontrolled nature of these spontaneous reports, a causal relationship to BuSpar has not been determined.

Drug Abuse and Dependence: *Controlled Substance Class*—Not a controlled substance.

***Physical and Psychological Dependence*—**Buspirone has shown no potential for abuse or diversion and there is no evidence that it causes tolerance, or either physical or psychological dependence. However, since it is difficult to predict from experiments the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of buspirone misuse or abuse (eg, development of tolerance, incrementation of dose, drug-seeking behavior).

Overdosage: *Signs and Symptoms*—At doses approaching 375 mg/day the following symptoms were observed: nausea, vomiting, dizziness, drowsiness, miosis, and gastric distress. No deaths have been reported in humans either with deliberate or accidental overdosage.

***Recommended Overdose Treatment*—**General symptomatic and supportive measures should be used along with immediate gastric lavage. No specific antidote is known and dialyzability of buspirone has not been determined.

For complete details, see Prescribing Information or consult your Mead Johnson Pharmaceuticals Representative.

U.S. Patent Nos. 3,717,634 and 4,182,763

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SPECIAL ARTICLE

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New Policy of Structured Abstracts

Effective with the January 1991 issue, *The American Journal of Psychiatry* will institute a policy of structured abstracts for Special Articles and Regular Articles. Authors of review articles must include the following information, under the headings indicated: *Objective*—the primary purpose of the review article; *Method*—data sources, study selection (the number of studies selected for review and how they were selected), data extraction (rules for abstracting data and how they were applied); *Results*—methods of data synthesis, key findings; and *Conclusions*—including potential applications and research needs. Authors of research articles must include *Objective*—questions addressed by the study; *Method*—design of the study, setting (location and level of clinical care), patients or participants (manner of selection and number who entered and completed the study), interventions (if any), main outcome measures (primary study outcome measure as planned before data collection); *Results*—key findings; and *Conclusions*—including direct clinical applications. Other types of articles, including Clinical and Research Reports, should include unstructured abstracts. Also effective with the January 1991 issue, the maximum number of words for abstracts for Special Articles and Regular Articles will be increased to 250 and for Clinical and Research Reports to 60.

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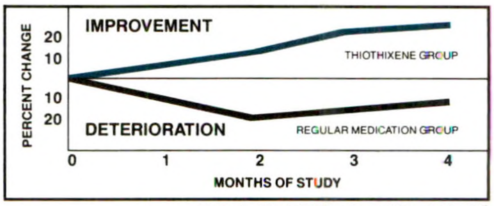
“IT FEELS GOOD TO FEEL USEFUL AGAIN”

For the chronic schizophrenic patient, Navane can mean more competent work performance,[1,2] and a smoother path towards social recovery. Navane may help improve the ability to concentrate, and promote a better attitude toward work and co-workers.[1-3]

Anticholinergic[4] and cardiovascular[5,6] side effects in patients treated with Navane are reported infrequently. Should extrapyramidal symptoms occur, they usually can be controlled.

27% rise in work output compared to baseline shown in patients switched to Navane[2,3]



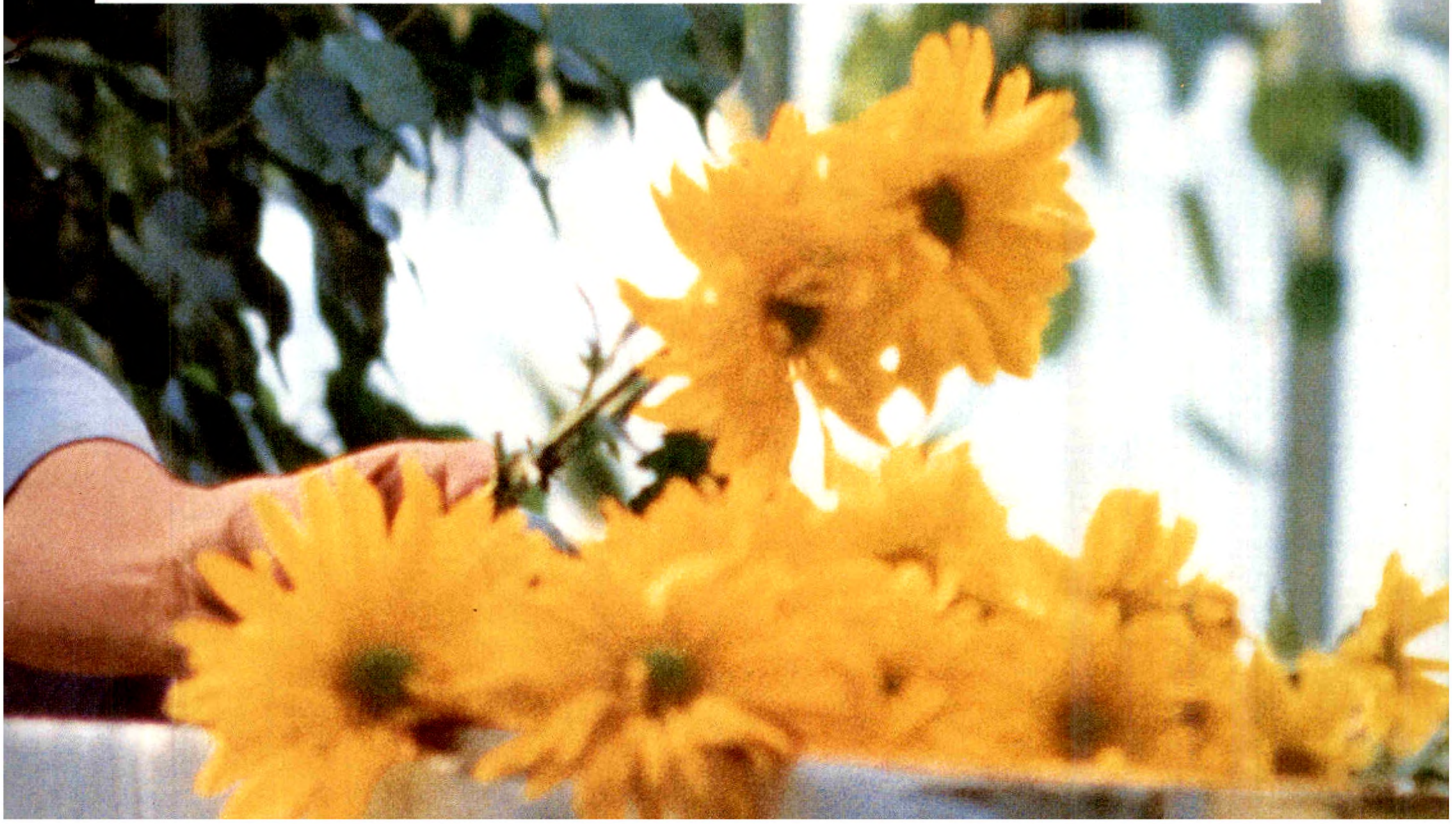
(Adapted from DiMascio and Demirgian[2,3])

Forty-two psychotic male and female patients under age 55 were entered in this study on a nonblind basis, and randomly assigned to their regular medication or switched to thiothixene. Patients were evaluated at baseline and on a daily basis, and periodically rated on the Global Improvement and Brief Psychiatric Rating Scales.

In schizophrenia,

Navane® (thiothixene)(thiothixene HCl)

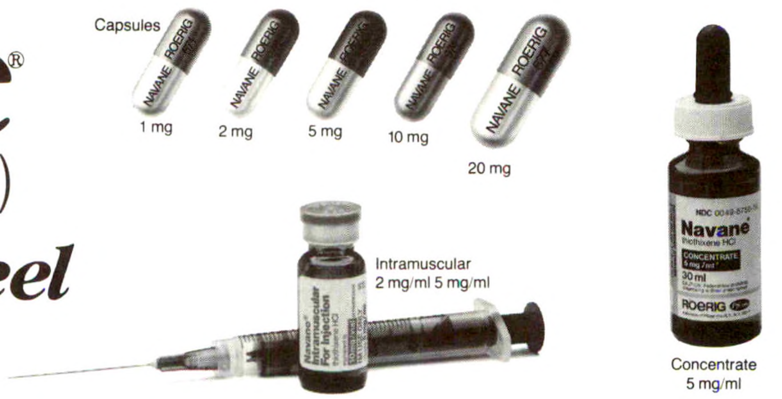
Please see brief summary of NAVANE® (thiothixene/thiothixene HCl) prescribing information on adjacent page.



Navane®

(thiothixene) (thiothixene HCl)

It feels good to feel useful again



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BRIEF SUMMARY OF PRESCRIBING INFORMATION
Navane® (thiothixene) Capsules: 1 mg, 2 mg, 5 mg, 10 mg, 20 mg
(thiothixene hydrochloride) Concentrate: 5 mg/ml, Intramuscular: 2 mg/ml, 5 mg/ml

Indications: Navane is effective in the management of manifestations of psychotic disorders. Navane has not been evaluated in the management of behavioral complications in patients with mental retardation.

Contraindications: Contraindicated in patients with circulatory collapse, comatose states, central nervous system depression due to any cause, and blood dyscrasias. Contraindicated in individuals who have shown hypersensitivity to the drug. It is not known whether there is a cross-sensitivity between the thioxanthenes and the phenothiazine derivatives, but the possibility should be considered.

Warnings: *Tardive Dyskinesia*—Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with neuroleptic (antipsychotic) drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of neuroleptic treatment, which patients are likely to develop the syndrome. Whether neuroleptic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of neuroleptic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if neuroleptic treatment is withdrawn. Neuroleptic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying disease process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, neuroleptics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic neuroleptic treatment should generally be reserved for patients who suffer from a chronic illness that, 1) is known to respond to neuroleptic drugs, and, 2) for whom alternative, equally effective, but potentially less harmful treatments are *not* available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on neuroleptics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

(For further information about the description of tardive dyskinesia and its clinical detection, please refer to Information for Patients in the Precautions section, and to the Adverse Reactions section.)

Neuroleptic Malignant Syndrome (NMS)—A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythimas).

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Usage in Pregnancy—Safe use of Navane during pregnancy has not been established. Therefore, this drug should be given to pregnant patients only when, in the judgment of the physician, the expected benefits from the treatment exceed the possible risks to mother and fetus. Animal reproduction studies and clinical experience to date have not demonstrated any teratogenic effects.

In the animal reproduction studies with Navane, there was some decrease in conception rate and litter size, and an increase in resorption rate in rats and rabbits, changes which have been similarly reported with other psychotropic agents. After repeated oral administration of Navane to rats (5 to 15 mg/kg/day), rabbits (3 to 50 mg/kg/day), and monkeys (1 to 3 mg/kg/day) before and during gestation, no teratogenic effects were seen. (See Precautions.)

Usage in Children—The use of Navane in children under 12 years of age is not recommended because safety and efficacy in the pediatric age group have not been established.

As is true with many CNS drugs, Navane may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery, especially during the first few days of therapy. Therefore, the patient should be cautioned accordingly.

As in the case of other CNS-acting drugs, patients receiving Navane should be cautioned about the possible additive effects (which may include hypotension) with CNS depressants and with alcohol.

Precautions: An antiemetic effect was observed in animal studies with Navane; since this effect may also occur in man, it is possible that Navane may mask signs of overdosage of toxic drugs and may obscure conditions such as intestinal obstruction and brain tumor.

In consideration of the known capability of Navane and certain other psychotropic drugs to precipitate convulsions, extreme caution should be used in patients with a history of convulsive disorders or those in a state of alcohol withdrawal since it may lower the convulsive threshold. Although Navane potentiates the actions of the barbiturates, the dosage of the anticonvulsant therapy should not be reduced when Navane is administered concurrently.

Caution as well as careful adjustment of the dosage is indicated when Navane is used in conjunction with other CNS depressants other than anticonvulsant drugs.

Though exhibiting rather weak anticholinergic properties, Navane should be used with caution in patients who are known or suspected to have glaucoma, or who might be exposed to extreme heat, or who are receiving atropine or related drugs.

Use with caution in patients with cardiovascular disease.

Also, careful observation should be made for pigmentary retinopathy, and lenticular pigmentation (fine lenticular pigmentation has been noted in a small number of patients treated with Navane for prolonged periods). Blood dyscrasias (agranulocytosis, pancytopenia, thrombocytopenic purpura), and liver damage (jaundice, biliary stasis) have been reported with related drugs.

Undue exposure to sunlight should be avoided. Photosensitive reactions have been reported in patients on Navane (thiothixene).

Intramuscular Administration—As with all intramuscular preparations, Navane Intramuscular should be injected well within the body of a relatively large muscle. The preferred sites are the upper outer quadrant of the buttock (i.e. gluteus maximus) and the mid-lateral thigh.

The deltoid area should be used only if well developed, such as in certain adults and older children, and then only with caution to avoid radial nerve injury. Intramuscular injections should not be made into the lower and mid-thirds of the upper arm. As with all intramuscular injections, aspiration is necessary to help avoid inadvertent injection into a blood vessel.

Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one third of human breast cancers are prolactin-dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

Information for Patients—Given the likelihood that some patients exposed chronically to neuroleptics will develop tardive dyskinesia, it is advised that all patients in whom chronic use is contemplated be given, if possible, full information about this risk. The decision to inform patients and/or their guardians must obviously take into account the clinical circumstances and the competency of the patient to understand the information provided.

Adverse Reactions: *Note:* Not all of the following adverse reactions have been reported with Navane (thiothixene). However, since Navane has certain chemical and pharmacologic similarities to the phenothiazines, all of the known side effects and toxicity associated with phenothiazine therapy should be borne in mind when Navane is used.

Cardiovascular effects: Tachycardia, hypotension, lightheadedness, and syncope. In the event hypotension occurs, epinephrine should not be used as a pressor agent since a paradoxical further lowering of blood pressure may result. Nonspecific EKG changes have been observed in some patients receiving Navane (thiothixene). These changes are usually reversible and frequently disappear on continued Navane therapy. The incidence of these changes is lower than that observed with some phenothiazines. The clinical significance of these changes is not known.

CNS effects: Drowsiness, usually mild, may occur although it usually subsides with continuation of Navane therapy. The incidence of sedation appears similar to that of the piperazine group of phenothiazines, but less than that of certain aliphatic phenothiazines. Restlessness, agitation and insomnia have been noted with Navane. Seizures and paradoxical exacerbation of psychotic symptoms have occurred with Navane infrequently.

Hyperreflexia has been reported in infants delivered from mothers having received structurally related drugs.

In addition, phenothiazine derivatives have been associated with cerebral edema and cerebrospinal fluid abnormalities.

Extrapyramidal symptoms, such as pseudo-parkinsonism, akathisia, and dystonia have been reported. Management of these extrapyramidal symptoms depends upon the type and severity. Rapid relief of acute symptoms may require the use of an injectable antiparkinson agent. More slowly emerging symptoms may be managed by reducing the dosage of Navane and/or administering an oral antiparkinson agent.

Persistent Tardive Dyskinesia: As with all antipsychotic agents tardive dyskinesia may appear in some patients on long-term therapy or may occur after drug therapy has been discontinued. The syndrome is characterized by rhythmical involuntary movements of the tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities.

Since early detection of tardive dyskinesia is important, patients should be monitored on an ongoing basis. It has been reported that fine vermicular movement of the tongue may be an early sign of the syndrome. If this or any other presentation of the syndrome is observed, the clinician should consider possible discontinuation of neuroleptic medication. (See Warnings section.)

Hepatic Effects: Elevations of serum transaminase and alkaline phosphatase, usually transient, have been infrequently observed in some patients. No clinically confirmed cases of jaundice attributable to Navane have been reported.

Hematologic Effects: As is true with certain other psychotropic drugs, leukopenia and leukocytosis, which are usually transient, can occur occasionally with Navane. Other antipsychotic drugs have been associated with agranulocytosis, eosinophilia, hemolytic anemia, thrombocytopenia and pancytopenia.

Allergic Reactions: Rash, pruritus, urticaria, photosensitivity and rare cases of anaphylaxis have been reported with Navane. Undue exposure to sunlight should be avoided. Although not experienced with Navane, exfoliative dermatitis and contact dermatitis (in nursing personnel) have been reported with certain phenothiazines.

Endocrine Disorders: Lactation, moderate breast enlargement and amenorrhea have occurred in a small percentage of females receiving Navane. If persistent, this may necessitate a reduction in dosage or the discontinuation of therapy. Phenothiazines have been associated with false positive pregnancy tests, gynecomastia, hypoglycemia, hyperglycemia, and glycosuria.

Autonomic Effects: Dry mouth, blurred vision, nasal congestion, constipation, increased sweating, increased salivation, and impotence have occurred infrequently with Navane therapy. Phenothiazines have been associated with miosis, mydriasis, and adynamic ileus.

Other Adverse Reactions: Hyperpyrexia, anorexia, nausea, vomiting, diarrhea, increase in appetite and weight, weakness or fatigue, polydipsia and peripheral edema.

Although not reported with Navane, evidence indicates there is a relationship between phenothiazine therapy and the occurrence of a systemic lupus erythematosus-like syndrome.

Neuroleptic Malignant Syndrome (NMS): Please refer to the text regarding NMS in the WARNINGS section.

NOTE: Sudden deaths have occasionally been reported in patients who have received certain phenothiazine derivatives. In some cases the cause of death was apparently cardiac arrest or asphyxia due to failure of the cough reflex. In others, the cause could not be determined nor could it be established that death was due to phenothiazine administration.

Dosage: Dosage of Navane should be individually adjusted depending on the chronicity and severity of the condition. See full prescribing information.

Overdosage: For information on signs and symptoms, and treatment of overdosage, see full prescribing information.

ROERIG Pfizer

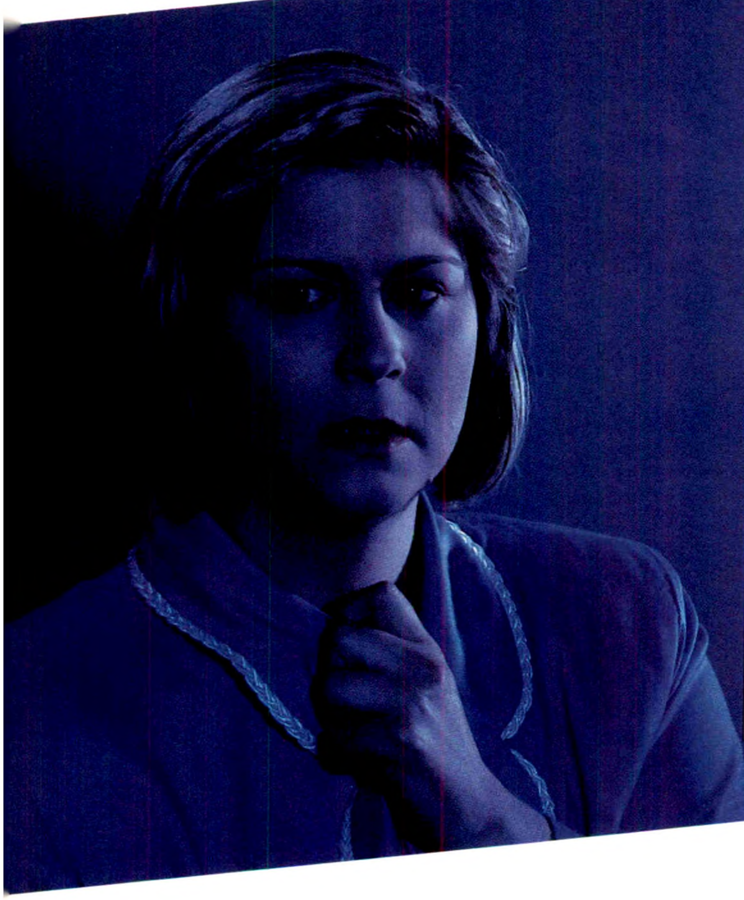
A division of Pfizer Pharmaceuticals
New York, New York 10017

Why doctors start with WELLBUTRIN® (bupropion HCl) instead of Prozac®* (fluoxetine HCl) for many patients.

* Prozac is a registered trademark of Dista Products Co., a division of Eli Lilly and Company.

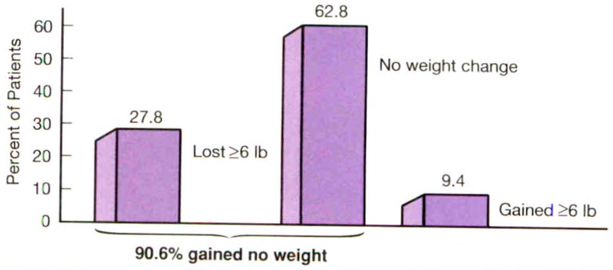
Kate's doctor wants a new-generation, non-serotonergic antidepressant which also causes little or no drowsiness or weight gain...

- Ninety percent of patients treated with WELLBUTRIN gained no weight.[1,2]
- The incidence of drowsiness is comparable to that of placebo.[3]



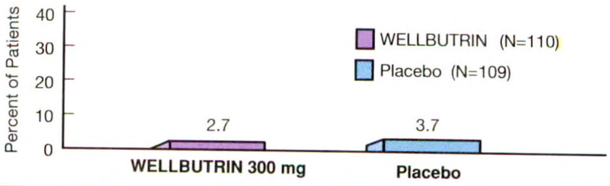
Relieves depression with little or no weight gain

Changes in Body Weight (N=341)[2]



Relieves depression with little or no daytime drowsiness

Incidence of Sedation[3]*



Start with non-serotonergic

Wellbutrin®

(BUPROPION HCl)

Relieves depression with few life-style disruptions

---

* As with all drugs in this category, patients should be cautioned that the ability to perform tasks requiring judgment or motor and cognitive skills may be impaired.

The overweight woman who couldn't stay awake

Name: Kate – Occupation: Legal assistant
Age: 33 – Height: 5'6" – Weight: 160 lb

Current History
Patient is hypersomnic, fatigued, and overweight. This current episode of depression has been going on for 14 months. She has difficulty functioning at work due to lack of concentration on the job.

Past history
Patient has a 15-year history of recurrent major depression and was hospitalized three times between the ages of 18 and 26. During a previous episode of 8 months' duration, she was unresponsive to a variety of antidepressants. Spontaneous remission of 5 months' duration followed.

Diagnosis: Depression

Prescribing considerations
Patient is overweight and also sleeps excessively.

Recommendation
Start WELLBUTRIN to relieve depression with little or no drowsiness or weight gain.

Outcome
At week 5, patient's depression appears to be improving. She reports feeling more energetic, with less daytime drowsiness, and reports not having gained any additional weight.

See brief summary of full prescribing information on last page of this advertisement.

Journal
102 Years of Service
Standing Broadened In Shareholder Suits
2d Circuit Restores Short-Swing Profit Claim
Group
Ruling

Every day doctors are choosing WELLBUTRIN instead of Prozac®* (fluoxetine HCl).

WELLBUTRIN is a unique new-generation antidepressant that:

- Effectively relieves depression with few life-style disruptions
- Is non-serotonergic[2,4-6]
- Has few cardiovascular effects[7-9]
- Causes few anticholinergic effects[2,3]
- Causes little or no weight gain[1,2]
- Causes little or no daytime drowsiness[3]
- Has minimal risk of sexual dysfunction[10]

The principal medically important adverse reaction with WELLBUTRIN is seizure, which occurs in approximately four-tenths of one percent of patients. This incidence may exceed that of other marketed antidepressants, although no direct comparative studies have been conducted. For more information about dosing to achieve optimal patient response and recommendations for reducing the risk of side effects, see full prescribing information, especially the DOSAGE AND ADMINISTRATION and WARNINGS sections.

References:

1. Harto-Truax N, Stern WC, Miller LL, Sato TL, Cato AE. Effects of bupropion on body weight. *J Clin Psychiatry.* 1983;44(5, sec 2):183-186. **2.** Data on file, Burroughs Wellcome Co., 1990. **3.** Lineberry CG, Johnston JA, Raymond RN, et al. A fixed-dose (300 mg) efficacy study of bupropion and placebo in depressed outpatients. *J Clin Psychiatry.* 1990;51:194-199. **4.** Shea VK, Wang CM. Bupropion (Wellbutrin) inhibits the firing rates of noradrenergic but not serotonergic neurons. *Soc Neurosci.* 1985;II:185. Abstract. **5.** Ferris RM, Cooper BR, Maxwell RA. Studies of bupropion's mechanism of antidepressant activity. *J Clin Psychiatry.* 1983;44(5, sec 2): 74-78. **6.** Richelson E. Synaptic pharmacology of antidepressants: an update. *McLean Hosp J.* 1988;XIII:67-88. **7.** Roose SP, Glassman AH, Giardina EGV, Johnson LL, Walsh BT, Bigger JT Jr. Cardiovascular effects of imipramine and bupropion in depressed patients with congestive heart failure. *J Clin Psychopharmacol.* 1987; 7:247-251. **8.** Farid FF, Wenger TL, Tsai SY, Singh BN, Stern WC. Use of bupropion in patients who exhibit orthostatic hypotension on tricyclic antidepressants. *J Clin Psychiatry.* 1983;44 (5, sec 2):170-173. **9.** Wenger TL, Cohn JB, Bustrack J. Comparison of the effects of bupropion and amitriptyline on cardiac conduction in depressed patients. *J Clin Psychiatry.* 1983;44(5, sec 2):174-175. **10.** Gardner EA, Johnston JA. Bupropion—an antidepressant without sexual pathophysiological action. *J Clin Psychopharmacol.* 1985;5:24-29.

The patient depicted in this advertisement is not an actual patient, but is a fictional composite of typical patient types.

Start with non-serotonergic

Wellbutrin®

(BUPROPION HCl)

Relieves depression with few life-style disruptions

* Prozac is a registered trademark of Dista Products Co., a division of Eli Lilly and Company.

Wellcome
Burroughs Wellcome Co.
Research Triangle Park, NC 27709

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Printed in U.S.A. WB-Y01644 October 1990

WELLBUTRIN® (BUPROPION HYDROCHLORIDE) Tablets

Before prescribing, please consult complete product information, a summary of which follows:

INDICATIONS AND USAGE: Wellbutrin is indicated for the treatment of depression. A physician considering the initiation of Wellbutrin should be aware that the drug may cause generalized seizures with an approximate incidence of 0.4% (4/1000). This incidence may exceed that of other antidepressants as much as fourfold. This relative risk is only an approximation since no direct comparative studies have been conducted.

CONTRAINDICATIONS: Wellbutrin is contraindicated in patients: with a seizure disorder; with a current or prior diagnosis of bulimia or anorexia nervosa, because of a higher incidence of seizures noted in such patients; who have shown an allergic response to it; or who are currently being treated with an MAO inhibitor. At least 14 days should elapse between discontinuation of an MAO inhibitor and initiation of treatment with Wellbutrin.

WARNINGS: SEIZURES: Wellbutrin is associated with seizures in approximately 0.4% (4/1000) of patients treated at doses up to 450 mg/day. This incidence of seizures may exceed that of other marketed antidepressants by as much as fourfold. This relative risk is only an approximate estimate because no direct comparative studies have been conducted. The estimated seizure incidence for Wellbutrin increases almost tenfold between 450 and 600 mg/day, which is twice the usually required daily dose (300 mg) and one and one-third the maximum recommended daily dose (450 mg). Given the wide variability among individuals and their capacity to metabolize and eliminate drugs, this disproportionate increase in seizure incidence with dose incrementation calls for caution in dosing.

During the initial development, 25 among approximately 2400 patients treated with Wellbutrin experienced seizures. At the time of seizure, 7 patients were receiving daily doses of 450 mg or below, for an incidence of 0.33% (3/1000) within the recommended dose range. Twelve (12) patients experienced seizures at 600 mg per day (2.3% incidence); 6 additional patients had seizures at daily doses between 600 and 900 mg (2.8% incidence).

A separate, prospective study was conducted to determine the incidence of seizure during an 8 week treatment exposure in approximately 3200 additional patients who received daily doses of up to 450 mg. Patients were permitted to continue treatment beyond 8 weeks if clinically indicated. Eight (8) seizures occurred during the initial 8 week treatment period and 5 seizures were reported in patients continuing treatment beyond 8 weeks, resulting in a total seizure incidence of 0.4%.

The risk of seizure appears to be strongly associated with dose and the presence of predisposing factors. A significant predisposing factor (e.g., history of head trauma or prior seizure, CNS tumor, concomitant medications that lower seizure threshold, etc.) was present in approximately one-half of the patients experiencing a seizure. Sudden and large increments in dose may contribute to increased risk. While many seizures occurred early in the course of treatment, some seizures did occur after several weeks at fixed dose.

***Recommendations for reducing the risk of seizure:* Retrospective analysis of clinical experience gained during the development of Wellbutrin suggests that the risk of seizure may be minimized if (1) the total daily dose of Wellbutrin does *not* exceed 450 mg, (2) the daily dose is administered t.i.d., with each single dose *not* to exceed 150 mg to avoid high peak concentrations of bupropion and/or its metabolites, and (3) the rate of incrementation of dose is very gradual. Extreme caution should be used when Wellbutrin is (1) administered to patients with a history of seizure, cranial trauma, or other predisposition(s) toward seizure, or (2) prescribed with other agents (e.g., antipsychotics, other antidepressants, etc.) or treatment regimens (e.g., abrupt discontinuation of a benzodiazepine) that lower seizure threshold.**

Potential for Hepatotoxicity: In rats receiving large doses of bupropion chronically, there was an increase in incidence of hepatic hyperplastic nodules and hepatocellular hypertrophy. In dogs receiving large doses of bupropion chronically, various histologic changes were seen in the liver, and laboratory tests suggesting mild hepatocellular injury were noted. Although scattered abnormalities in liver function tests were detected in patients participating in clinical trials, there is no clinical evidence that bupropion acts as a hepatotoxin in humans.

PRECAUTIONS: General:

Agitation and Insomnia: A substantial proportion of patients treated with Wellbutrin experience some degree of increased restlessness, agitation, anxiety, and insomnia, especially shortly after initiation of treatment. In clinical studies, these symptoms were sometimes of sufficient magnitude to require treatment with sedative/hypnotic drugs. In approximately 2% of patients, symptoms were sufficiently severe to require discontinuation of Wellbutrin treatment.

Psychosis, Confusion, and Other Neuropsychiatric Phenomena: Patients treated with Wellbutrin have been reported to show a variety of neuropsychiatric signs and symptoms including delusions, hallucinations, psychotic episodes, confusion, and paranoia. Because of the uncontrolled nature of many studies, it is impossible to provide a precise estimate of the extent of risk imposed by treatment with Wellbutrin. In several cases, neuropsychiatric phenomena abated upon dose reduction and/or withdrawal of treatment.

Activation of Psychosis and/or Mania: Antidepressants can precipitate manic episodes in Bipolar Manic Depressive patients during the depressed phase of their illness and may activate latent psychosis in other susceptible patients. Wellbutrin is expected to pose similar risks.

Altered Appetite and Weight: A weight loss of greater than 5 pounds occurred in 28% of Wellbutrin patients. This incidence is approximately double that seen in comparable patients treated with tricyclics or placebo. Furthermore, while 34.5% of patients receiving tricyclic antidepressants gained weight, only 9.4% of patients treated with Wellbutrin did. Consequently, if weight loss is a major presenting sign of a patient's depressive illness, the anorectic and/or weight reducing potential of Wellbutrin should be considered.

Suicide: The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Accordingly, prescriptions for Wellbutrin should be written for the smallest number of tablets consistent with good patient management.

Use in Patients with Systemic Illness: There is no clinical experience establishing the safety of Wellbutrin in patients with a recent history of myocardial infarction or unstable heart disease. Therefore, care should be exercised if it is used in these groups.

Because bupropion HCl and its metabolites are almost completely excreted through the kidney and metabolites are likely to undergo conjugation in the liver prior to urinary excretion, treatment of patients with renal or hepatic impairment should be initiated at reduced dosage as bupropion and its metabolites may accumulate in such patients beyond concentrations expected in patients without renal or hepatic impairment. The patient should be closely monitored for possible toxic effects of elevated blood and tissue levels of drug and metabolites.

Information for Patients: Consult complete product information.

Drug Interactions: No systematic data have been collected on the consequences of the concomitant administration of Wellbutrin and other drugs.

However, animal data suggest that Wellbutrin may be an inducer of drug metabolizing enzymes. This may be of potential clinical importance because the blood levels of co-administered drugs may be altered.

Alternatively, because bupropion is extensively metabolized, the co-administration of other drugs may affect its clinical activity. In particular, care should be exercised when administering drugs known to affect hepatic drug metabolizing enzyme systems (e.g., carbamazepine, cimetidine, phenobarbital, phenytoin).

Studies in animals demonstrate that the acute toxicity of bupropion is enhanced by the MAO inhibitor phenelzine (see CONTRAINDICATIONS).

Limited clinical data suggest a higher incidence of adverse experiences in patients receiving concurrent administration of Wellbutrin and L-dopa. Administration of Wellbutrin to patients receiving L-dopa concurrently should be undertaken with caution, using small initial doses and small gradual dose increases.

Concurrent administration of Wellbutrin and agents which lower seizure threshold should be undertaken only with extreme caution (see WARNINGS). Low initial dosing and small gradual dose increases should be employed.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Lifetime carcinogenicity studies were performed in rats and mice at doses up to 300 and 150 mg/kg/day, respectively. In the rat study there was an increase in nodular proliferative lesions of the liver at doses of 100 to 300 mg/kg/day; lower doses were not tested. The question of whether or not such lesions may be precursors of neoplasms of the liver is currently unresolved. Similar liver lesions were not seen in the mouse study, and no increase in malignant tumors of the liver and other organs was seen in either study.

Bupropion produced a borderline positive response (2-3 times control mutation rate) in some strains in the Ames bacterial mutagenicity test, and a high oral dose (300, but not 100 or 200 mg/kg) produced a low incidence of chromosomal aberrations in rats. The relevance of these results in estimating the risk of human exposure to therapeutic doses is unknown.

A fertility study was performed in rats; no evidence of impairment of fertility was encountered at oral doses up to 300 mg/kg/day.

Pregnancy: ***Teratogenic Effects:*** Pregnancy Category B: Reproduction studies have been performed in rabbits and rats at doses up to 15-45 times the human daily dose and have revealed no definitive evidence of impaired fertility or harm to the fetus due to bupropion. (In rabbits, a slightly increased incidence of fetal abnormalities was seen in two studies, but there was no increase in any specific abnormality). There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery: The effect of Wellbutrin on labor and delivery in humans is unknown.

Nursing Mothers: Because of the potential for serious adverse reactions in nursing infants from Wellbutrin, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: The safety and effectiveness of Wellbutrin in individuals under 18 years old have not been established.

Use in the Elderly: Wellbutrin has not been systematically evaluated in older patients.

ADVERSE REACTIONS: (See also WARNINGS and PRECAUTIONS) Adverse events commonly encountered in patients treated with Wellbutrin are agitation, dry mouth, insomnia, headache/migraine, nausea/vomiting, constipation, and tremor.

Adverse events were sufficiently troublesome to cause discontinuation of Wellbutrin treatment in approximately ten percent of the 2400 patients and volunteers who participated in clinical trials during the product's initial development. The more common events causing discontinuation include neuropsychiatric disturbances (3.0%), primarily agitation and abnormalities in mental status; gastrointestinal disturbances (2.1%), primarily nausea and vomiting; neurological disturbances (1.7%), primarily seizures, headaches, and sleep disturbances; and dermatologic problems (1.4%), primarily rashes. It is important to note, however, that many of these events occurred at doses that exceed the recommended daily dose.

The table below is presented solely to indicate the relative frequency of adverse events reported in representative controlled clinical studies conducted to evaluate the safety and efficacy of Wellbutrin under relatively similar conditions of daily dosage (300-600 mg), setting, and duration (3-4 weeks). The figures cited cannot be used to predict precisely the incidence of untoward events in the course of usual medical practice where patient characteristics and other factors must differ from those which prevailed in the clinical trials. These incidence figures also cannot be compared with those obtained from other clinical studies involving related drug products as each group of drug trials is conducted under a different set of conditions.

Finally, it is important to emphasize that the tabulation does not reflect the relative severity and/or clinical importance of the events. A better perspective on the serious adverse events associated with the use of Wellbutrin is provided in the WARNINGS and PRECAUTIONS sections.

TREATMENT EMERGENT ADVERSE EXPERIENCE INCIDENCE IN PLACEBO-CONTROLLED CLINICAL TRIALS*
(Percent of Patients Reporting)

Adverse Experience	Wellbutrin Patients (n = 323)	Placebo Patients (n = 185)
CARDIOVASCULAR		
Cardiac Arrhythmias	5.3	4.3
Dizziness	22.3	16.2
Hypertension	4.3	1.6
Hypotension	2.5	2.2
Palpitations	3.7	2.2
Syncope	1.2	0.5
Tachycardia	10.8	8.6
DERMATOLOGIC		
Pruritus	2.2	0.0
Rash	8.0	6.5
GASTROINTESTINAL		
Anorexia	18.3	18.4
Appetite Increase	3.7	2.2
Constipation	26.0	17.3
Diarrhea	6.8	8.6
Dyspepsia	3.1	2.2
Nausea/Vomiting	22.9	18.9
Weight Gain	13.6	22.7
Weight Loss	23.2	23.2
GENITOURINARY		
Impotence	3.4	3.1
Menstrual Complaints	4.7	1.1
Urinary Frequency	2.5	2.2
Urinary Retention	1.9	2.2
MUSCULOSKELETAL		
Arthritis	3.1	2.7
NEUROLOGICAL		
Akathisia	1.5	1.1
Akinesia/Bradykinesia	8.0	8.6
Cutaneous Temperature Disturbance	1.9	1.6
Dry Mouth	27.6	18.4
Excessive Sweating	22.3	14.6
Headache/Migraine	25.7	22.2
Impaired Sleep Quality	4.0	1.6
Increased Salivary Flow	3.4	3.8
Insomnia	18.6	15.7
Muscle Spasms	1.9	3.2
Pseudoparkinsonism	1.5	1.6
Sedation	19.8	19.5
Sensory Disturbance	4.0	3.2
Tremor	21.1	7.6
NEUROPSYCHIATRIC		
Agitation	31.9	22.2
Anxiety	3.1	1.1
Confusion	8.4	4.9
Decreased Libido	3.1	1.6
Delusions	1.2	1.1
Disturbed Concentration	3.1	3.8
Euphoria	1.2	0.5
Hostility	5.6	3.8
NONSPECIFIC		
Fatigue	5.0	8.6
Fever/Chills	1.2	0.5
RESPIRATORY		
Upper Respiratory Complaints	5.0	11.4
SPECIAL SENSES		
Auditory Disturbance	5.3	3.2
Blurred Vision	14.6	10.3
Gustatory Disturbance	3.1	1.1

*Events reported by at least 1% of Wellbutrin patients are included.

Other events observed during the development of Wellbutrin: The conditions and duration of exposure to Wellbutrin varied greatly and a substantial proportion of the experience was gained in open and uncontrolled clinical settings. During this experience, numerous adverse events were reported; however, without appropriate controls, it is impossible to determine with certainty which events were or were not caused by Wellbutrin. The following enumeration is organized by organ system and describes events in terms of their relative frequency of reporting in the data base. Events of major clinical importance are also described in the WARNINGS and PRECAUTIONS sections of the labeling.

The following definitions of frequency are used: Frequent adverse events are defined as those occurring in at least 1/100 patients. Infrequent adverse events are those occurring in 1/100 to 1/1000 patients, while rare events are those occurring in less than 1/1000 patients.

Cardiovascular: Frequent was edema; infrequent were chest pain, EKG abnormalities (premature beats and nonspecific ST-T changes), and shortness of breath/dyspnea; rare were flushing, pallor, phlebitis and myocardial infarction.

Dermatologic: Frequent were nonspecific rashes; infrequent were alopecia and dry skin; rare were change in hair color, hirsutism and acne.

Endocrine: Infrequent was gynecomastia; rare were glycosuria and hormone level change.

Gastrointestinal: Infrequent were dysphagia, thirst disturbance, and liver damage/jaundice; rare were rectal complaints, colitis, G.I. bleeding, intestinal perforation and stomach ulcer.

Genitourinary: Frequent was nocturia; infrequent were vaginal irritation, testicular swelling, urinary tract infection, painful erection, and retarded ejaculation; rare were dysuria, enuresis, urinary incontinence, menopause, ovarian disorder, pelvic infection, cystitis, dyspareunia, and painful ejaculation.

Hematologic/Oncologic: Rare were lymphadenopathy, anemia and pancytopenia.

Musculoskeletal: Rare was musculoskeletal chest pain.

Neurological: (see WARNINGS) Frequent were ataxia/incoordination, seizure, myoclonus, dyskinesia, and dystonia; infrequent were mydriasis, vertigo, and dysarthria; rare were EEG abnormality, abnormal neurological exam, impaired attention, sciatica and aphasia.

Neuropsychiatric: (see PRECAUTIONS) Frequent were mania/hypomania, increased libido, hallucinations, decrease in sexual function, and depression; infrequent were memory impairment, depersonalization, psychosis, dysphoria, mood instability, paranoia, formal thought disorder, and frigidity; rare was suicidal ideation.

Oral Complaints: Frequent was stomatitis; infrequent were toothache, bruxism, gum irritation, and oral edema; rare was glossitis.

Respiratory: Infrequent were bronchitis and shortness of breath/dyspnea; rare were epistaxis, rate or rhythm disorder, pneumonia and pulmonary embolism.

Special Senses: Infrequent was visual disturbance; rare was diplopia.

Nonspecific: Frequent were flu-like symptoms; infrequent was nonspecific pain; rare were body odor, surgically related pain, infection, medication reaction and overdose.

DOSAGE AND ADMINISTRATION: General Dosing Considerations: It is particularly important to administer Wellbutrin in a manner most likely to minimize the risk of seizure (see WARNINGS). Increases in dose should not exceed 100 mg/day in a 3 day period. Gradual escalation in dosage is also important if agitation, motor restlessness, and insomnia, often seen during the initial days of treatment, are to be minimized. If necessary, these effects may be managed by temporary reduction of dose or the short-term administration of an intermediate to long-acting sedative hypnotic. A sedative hypnotic usually is not required beyond the first week of treatment. Insomnia may also be minimized by avoiding bedtime doses. If distressing, untoward effects supervene, dose escalation should be stopped.

No single dose of Wellbutrin should exceed 150 mg. Wellbutrin should be administered t.i.d., preferably with at least 6 hours between successive doses.

Usual Dosage for Adults: The usual adult dose is 300 mg/day, given t.i.d. Dosing should begin at 200 mg/day, given as 100 mg b.i.d. Based on clinical response, this dose may be increased to 300 mg/day, given as 100 mg t.i.d., no sooner than 3 days after beginning therapy (see table below).

Dosing Regimen

Treatment Day	Total Daily Dose	Tablet Strength	Number of Tablets		
			Morning	Midday	Evening
1	200 mg	100 mg	1	0	1
4	300 mg	100 mg	1	1	1

Increasing the Dosage Above 300 mg/Day: As with other antidepressants, the full antidepressant effect of Wellbutrin may not be evident until 4 weeks of treatment or longer. An increase in dosage, up to a maximum of 450 mg/day, given in divided doses of not more than 150 mg each, may be considered for patients in whom no clinical improvement is noted after several weeks of treatment at 300 mg/day. Dosing above 300 mg/day may be accomplished using the 75 or 100 mg tablets. The 100 mg tablet must be administered q.i.d. with at least 4 hours between successive doses, in order not to exceed the limit of 150 mg in a single dose. Wellbutrin should be discontinued in patients who do not demonstrate an adequate response after an appropriate period of treatment at 450 mg/day.

Elderly Patients: In general, older patients are known to metabolize drugs more slowly and to be more sensitive to the anticholinergic, sedative, and cardiovascular side effects of antidepressant drugs.

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Childhood Traumas: An Outline and Overview

By Lenore C. Terr

Calendar

For free listing of your organization's official annual or regional meeting, please send us the following information: sponsor, location, inclusive dates, type and number of continuing education credits (if available), and the name, address, and telephone number of the person or group to contact for more information. All notices and changes must be received no later than 120 days before the first day of the month of desired publication and should be addressed to Calendar, American Journal of Psychiatry, *1400 K St., N.W., Washington, DC 20005. Because of space limitations, only listings of meetings of the greatest interest to* Journal *readers will be included.*

FEBRUARY

February 1–2, conference, "Child/Adolescent/Adult Suicide," Cambridge Hospital and Harvard Medical School, Boston. Contact: Judy Reiner Platt, Cambridge Hospital, 1493 Cambridge Street, Cambridge, MA 02139; 617-864-6165.

February 10–13, annual meeting, American Association of Psychiatric Services for Children, Miami Beach, Fla. Contact: Sydney Koret, Ph.D., 1200C Scottsville Road, Suite 225, Rochester, NY 14624; 716-235-6910.

February 14–19, annual meeting, American Association for the Advancement of Science, Washington, D.C. Contact: Meetings Office, 1333 H Street, N.W., Washington, DC 20005; 202-326-6448.

February 15–17, conference, "Practical Psychodynamic Psychiatry in the 1990s," Continuing Medical Education, Inc., Orlando, Fla. Contact: Janell Parque, Program Director, 730 El Camino Way, Tustin, CA 92680; 800-447-4474.

February 16–18, annual meeting, American Association for Geriatric Psychiatry, Fort Lauderdale, Fla. Contact: George T. Grossberg, M.D., President, P.O. Box 376A, Greenbelt, MD 20768; 301-220-0952.

February 18–23, annual meeting, American Group Psychotherapy Association, Inc., San Antonio, Tex. Contact: Marsha S. Block, Chief Executive Officer, 25 East 21st Street, 6th Floor, New York, NY 10010; 212-477-2677.

February 21–24, American Society on Addiction Medicines' Fifth National Forum on AIDS and Chemical Dependency, San Francisco. Contact: Meeting and Travel Services, Inc. 404-458-3382.

February 22–23, 1st European Symposium on Drug Addiction and AIDS, Vienna. Contact Dr. Norbert Loimer, Waehringer Guertel 18-20, A-1090 Vienna, Austria; 43-1-40400-35 75.

February 26–March 1, annual meeting, Child Welfare League of America, Inc., Washington, D.C. Contact: David S. Liederman, Executive Director, 440 1st Street, N.W., Suite 310, Washington, DC 20001; 202-638-2952.

February 27–March 3, annual meeting, American Society for Psychosomatic Obstetrics and Gynecology, Houston, Tex. Contact: Gail Robinson, M.D., Toronto General Hospital, 200 Elizabeth Street, Toronto, Ontario, Canada M5G 2C4; 416-340-4048.

February 28–March 2, annual meeting, American College of Mental Health Administration, Napa, Calif. Contact: Lawrence A. Heller, M.D., 225 W. Swissvale Avenue, Pittsburgh, PA 15218-1632; 412-244-0670.

MARCH

March 6–9, annual meeting, Association for Academic Psychiatry, Tampa, Fla. Contact Ms. O'Loughlin, Dept. of Psychiatry, Mount Auburn Hospital, Cambridge, MA 02238; 617-499-5198.

March 7–9, annual meeting, American Psychopathological Association, New York. Contact: Katherine A. Halmi, M.D., President, 21 Bloomingdale Road, White Plains, NY 10605; 914-997-5875.

March 7–9, conference, "Recent Advances in Geriatric Medicine: New Treatment Options for Old Problems," University of California, San Diego, Department of Medicine. Contact: Cass Jones, Professional Conference Management, Inc., 7916 Convoy Court, San Diego, CA 92111; 619-565-9921.

March 8–9, conference, "Treating the Addictions," Cambridge Hospital and Harvard Medical School, Boston. Contact: Judy Reiner Platt, Cambridge Hospital, 1493 Cambridge Street, Cambridge, MA 02139; 617-864-6165.

March 14–16, annual meeting, American Psychosomatic Society, Santa Fe, N.Mex. Contact: Carol Ann Kiner, Associate Director, American Psychosomatic Society, 6728 Old McLean Village Drive, McLean, VA 22101; 703-556-9222.

March 15–17, conference, "Psychopharmacology for the Primary Care Physician," University of California, San Diego, Department of Psychiatry. Contact: Cass Jones, Professional Conference Management, Inc., 7916 Convoy Court, San Diego, CA 92111; 619-565-9921.

March 20–23, annual meeting, Society of Behavioral Medicine, Washington, D.C. Contact Judith C. Woodward, Ex-

(Continued on page A28)

PAMELOR® (nortriptyline HCl)
BRIEF SUMMARY.
Please see package insert for full prescribing information.

Contraindications: 1) Concurrent use with a monoamine oxidase (MAO) inhibitor, since hyperpyretic crises, severe convulsions, and fatalities have occurred when similar tricyclic antidepressants were used in such combinations; MAO inhibitors should be discontinued for at least two weeks before treatment with Pamelor® (nortriptyline HCl) is started. 2) Hypersensitivity to Pamelor® (nortriptyline HCl), cross-sensitivity with other dibenzazepines is a possibility. 3) The acute recovery period after myocardial infarction.

Warnings: Give only under close supervision to patients with cardiovascular disease, because of the tendency of the drug to produce sinus tachycardia and to prolong conduction time; myocardial infarction, arrhythmia, and strokes have occurred. The antihypertensive action of guanethidine and similar agents may be blocked. Because of its anticholinergic activity, nortriptyline should be used with great caution in patients who have glaucoma or a history of urinary retention. Patients with a history of seizures should be followed closely, since nortriptyline is known to lower the convulsive threshold. Great care is required in hyperthyroid patients or those receiving thyroid medication, since cardiac arrhythmias may develop. Nortriptyline may impair the mental and/or physical abilities required for the performance of hazardous tasks, such as operating machinery or driving a car; therefore, the patient should be warned accordingly. Excessive consumption of alcohol may have a potentiating effect, which may lead to the danger of increased suicidal attempts or overdosage, especially in patients with histories of emotional disturbances or suicidal ideation.

The concomitant administration of quinidine and nortriptyline may result in a significantly longer plasma half-life, higher A.U.C. and lower clearance of nortriptyline.

Use in Pregnancy—Safe use during pregnancy and lactation has not been established; therefore, in pregnant patients, nursing mothers, or women of childbearing potential, the potential benefits must be weighed against the possible hazards.

Use in Children—Not recommended for use in children, since safety and effectiveness in the pediatric age group have not been established.

Precautions: Use in schizophrenic patients may result in an exacerbation of the psychosis or may activate latent schizophrenic symptoms; in overactive or agitated patients, increased anxiety and agitation may occur; in manic-depressive patients, symptoms of the manic phase may emerge. Administration of reserpine during therapy with a tricyclic antidepressant has been shown to produce a "stimulating" effect in some depressed patients. Troublesome patient hostility may be aroused. Epileptiform seizures may accompany administration. Close supervision and careful adjustment of dosage are required when used with other anticholinergic drugs and sympathomimetic drugs. Concurrent administration of cimetidine can produce clinically significant increases in the plasma concentrations of the tricyclic antidepressant. Patients should be informed that the response to alcohol may be exaggerated. When essential, may be administered with electroconvulsive therapy, although the hazards may be increased. Discontinue the drug for several days, if possible, prior to elective surgery. The possibility of a suicidal attempt by a depressed patient remains after the initiation of treatment; in this regard, it is important that the least possible quantity of drug be dispensed at any given time. Both elevation and lowering of blood sugar levels have been reported. A case of significant hypoglycemia has been reported in a type II diabetic patient maintained on chlorpropamide (250 mg/day), after the addition of nortriptyline (125 mg/day).

Adverse Reactions: *Cardiovascular*—Hypotension, hypertension, tachycardia, palpitation, myocardial infarction, arrhythmias, heart block, stroke. *Psychiatric*—Confusional states (especially in the elderly) with hallucinations, disorientation, delusions; anxiety, restlessness, agitation; insomnia, panic, nightmares; hypomania; exacerbation of psychosis. *Neurologic*—Numbness, tingling, paresthesias of extremities; incoordination, ataxia, tremors; peripheral neuropathy; extrapyramidal symptoms; seizures, alteration in EEG patterns; tinnitus. *Anticholinergic*—Dry mouth and, rarely, associated sublingual adenitis; blurred vision, disturbance of accommodation, mydriasis; constipation, paralytic ileus; urinary retention, delayed micturition, dilation of the urinary tract. *Allergic*—Skin rash, petechiae, urticaria, itching, photosensitization (avoid excessive exposure to sunlight); edema (general or of face and tongue), drug fever, cross-sensitivity with other tricyclic drugs. *Hematologic*—Bone marrow depression, including agranulocytosis; eosinophilia; purpura; thrombocytopenia. *Gastrointestinal*—Nausea and vomiting, anorexia, epigastric distress, diarrhea, peculiar taste, stomatitis, abdominal cramps, black-tongue. *Endocrine*—Gynecomastia in the male, breast enlargement and galactorrhea in the female; increased or decreased libido, impotence; testicular swelling; elevation or depression of blood sugar levels; syndrome of inappropriate ADH (antidiuretic hormone) secretion. *Other*—Jaundice (simulating obstructive), altered liver function; weight gain or loss; perspiration; flushing; urinary frequency, nocturia; drowsiness, dizziness, weakness, fatigue; headache; parotid swelling; alopecia. *Withdrawal Symptoms*—Though these are not indicative of addiction, abrupt cessation of treatment after prolonged therapy may produce nausea, headache, and malaise.

Overdosage: Toxic overdosage may result in confusion, restlessness, agitation, vomiting, hyperpyrexia, muscle rigidity, hyperactive reflexes, tachycardia, ECG evidence of impaired conduction, shock, congestive heart failure, stupor, coma, and CNS stimulation with convulsions followed by respiratory depression. Deaths have occurred with drugs of this class. No specific antidote is known; general supportive measures are indicated, with gastric lavage. [PAM-Z19—9/1/89]

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Postgraduate Psychiatry: Clinical and Scientific Foundations, edited by Louis Appleby, B.Sc.(Hons.), M.R.C.P., M.R.C.Psych., and David Michael Forshaw, M.R.C.Psych., D.H.M.S.A., D.P.M.S.A. Oxford, Heinemann Medical Books (Stoneham, Mass., Butterworths, distributor), 1990, 505 pp., $65.00 (paper).

The Feeling Good Handbook (1989), by David D. Burns, M.D. New York, Plume, 1990, 570 pp., $10.95 (paper).

Anxiety and the Heart, edited by D.G. Byrne and Ray H. Rosenman. New York, Hemisphere Publishing Corp. (Taylor & Francis Group), 1990, 491 pp., no price listed.

Co-Dependency: Issues in Treatment and Recovery: Alcoholism Treatment Quarterly, vol. 6, number 1, 1989, edited by Bruce Carruth and Warner Mendenhall. New York, Haworth Press, 1989, 167 pp., $29.95; $17.95 (paper).

The Sexually Unusual: Guide to Understanding and Helping: Journal of Social Work and Human Sexuality, vol. 7, number 1, 1988, edited by Dennis M. Dailey. New York, Haworth Press, 1988, 166 pp., $29.95.

You'll See It When You Believe It: The Way to Your Personal Transformation (1989), by Dr. Wayne W. Dyer. New York, Avon Books, 1990, 262 pp., $4.95 (paper).

Essential Papers on Transference, edited by Aaron H. Esman, M.D. New York, New York University Press, 1990, 528 pp., $25.00 (paper).

The Neurotic Child and Adolescent, edited by M. Hossein Etezady, M.D. Northvale, N.J., Jason Aronson, 1990, 411 pp., $50.00.

Adolescent Psychiatry: Developmental and Clinical Studies, vol. 17: Annals of the American Society for Adolescent Psychiatry, edited by Sherman C. Feinstein, Aaron H. Esman, John G. Looney, George H. Orvin, John L. Schimel, Allan Z. Schwartzberg, Arthur D. Sorosky, and Max Sugar. Chicago, University of Chicago Press, 1990, 544 pp., $40.00.

The Story of Anna O. (1972), by Lucy Freeman. New York, Paragon House, 1990, 268 pp., $10.95 (paper).

Control Your Dreams: How Lucid Dreaming Can Help You Uncover Your Hidden Desires, Confront Your Hidden Fears, and Explore the Frontiers of Human Consciousness (1989), by Jayne Gackenbach and Jane Bosveld. New York, Harper Perennial (HarperCollins), 1990, 226 pp., $8.95 (paper).

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Breaking New Ground for Youth at Risk: Program Summaries: OSAP Technical Report 1, edited by Eric N. Goplerud, Ph.D. Rockville, Md., Office for Substance Abuse Prevention, U.S. Department of Health and Human Services, 1990, 137 pp., no charge (paper).

Alcohol Research From Bench to Bedside: Advances in Alcohol and Substance Abuse, vol. 7, numbers 3/4, 1988, edited by Barry Stimmel, M.D. New York, Haworth Press, 1989, 257 pp., $39.95.

Being Homosexual: Gay Men and Their Development (1989), by Richard A. Isay, M.D. New York, Avon Books, 1990, 149 pp., $7.95 (paper).

Madness in the Streets: How Psychiatry and the Law Abandoned the Mentally Ill, by Rael Jean Isaac and Virginia C. Armat. New York, Free Press (Macmillan), 1990, 414 pp., $24.95.

Calling It a Day: Daily Meditations for Workaholics, by Robert Larrañaga. San Francisco, Harper & Row, 1990, 370 pp., $8.95 (paper).

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Creative Medical Teaching, by Neal Whitman, M.P.A., Ed.D. Salt Lake City, Department of Family and Preventive Medicine, University of Utah, 1990, 228 pp., $24.00.

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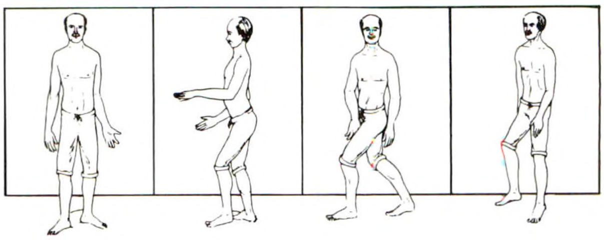

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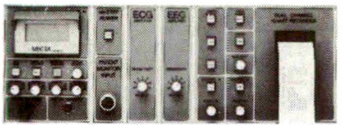

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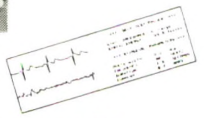

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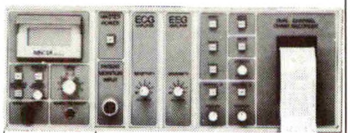

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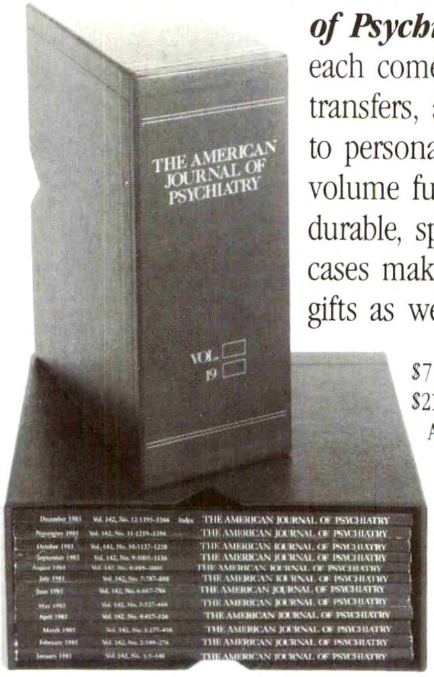

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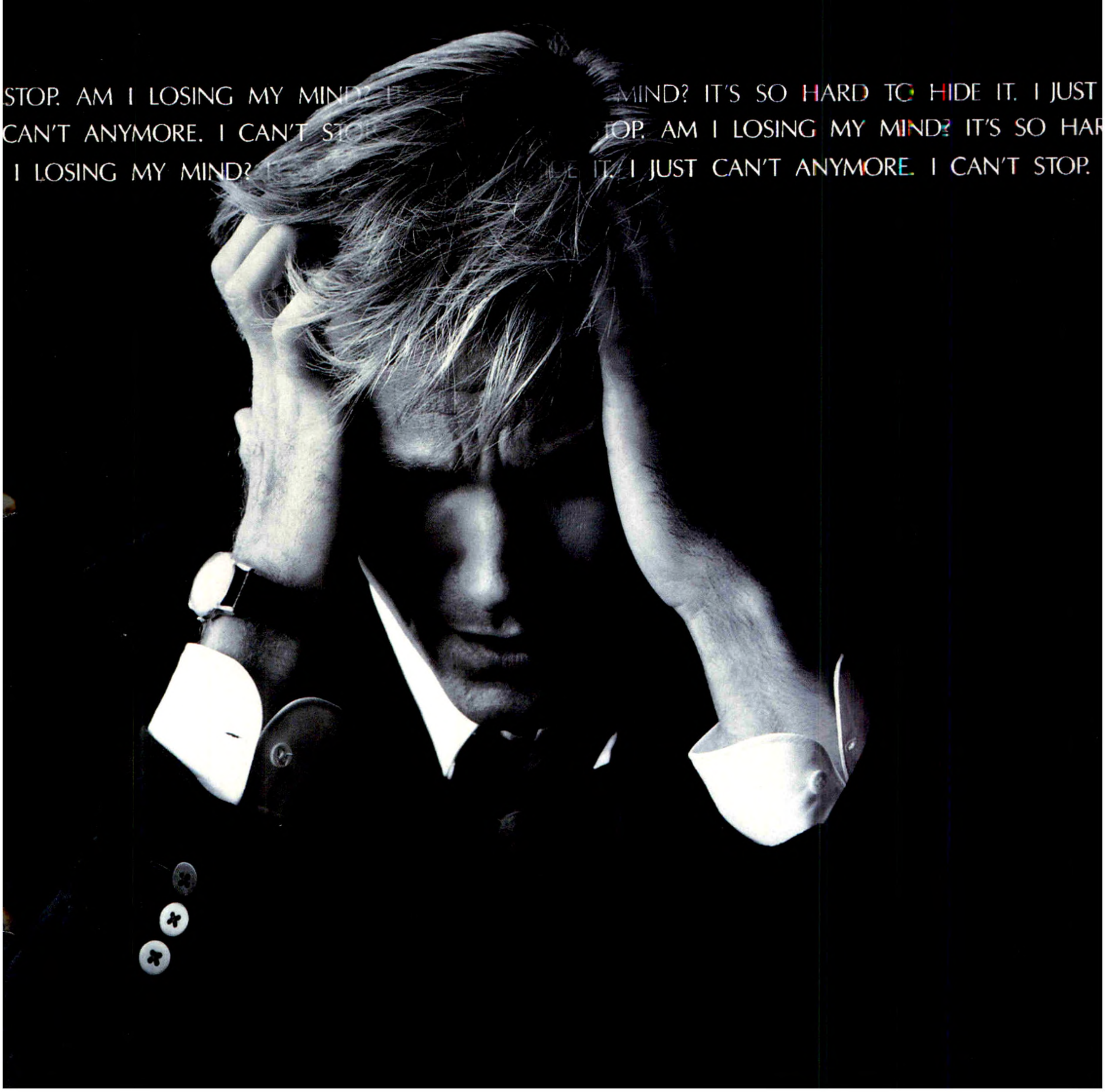
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References: 1. *DeVeaugh-Geiss J, Landau P, Katz R. Treatment of obsessive-compulsive disorder with clomipramine.* Psychiatr Ann. *1989;19:97-101.* **2.** *Insel TR, Murphy DL, Cohen RM et al. Obsessive-compulsive disorder: A double-blind trial of clomipramine and clorgyline.* Arch Gen Psychiatry. *1983;40:605-611.* **3.** *Zohar J, Insel TR, Zohar-Kadouch RC et al. Serotonergic responsivity in obsessive-compulsive disorder.* Arch Gen Psychiatry. *1988;45:167-171.* **4.** *Data on file, CIBA-GEIGY Corporation.*

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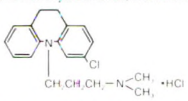
Prescribing Information

DESCRIPTION

Anafranil, clomipramine hydrochloride, is an anti-obsessional drug that belongs to the class (dibenzazepine) of pharmacologic agents known as tricyclic antidepressants. Anafranil is available as capsules of 25, 50, and 75 mg for oral administration.

Clomipramine hydrochloride is 3-chloro-5-[3-(dimethylamino)propyl]-10,11-dihydro-5H-dibenz[b,f]azepine monohydrochloride, and its structural formula is:



Clomipramine hydrochloride is a white to off-white crystalline powder. It is freely soluble in water, in methanol, and in methylene chloride, and insoluble in ethyl ether and in hexane. Its molecular weight is 351.3.

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CLINICAL PHARMACOLOGY

Pharmacodynamics

Clomipramine (CMI) is presumed to influence obsessive and compulsive behaviors through its effects on serotonergic neuronal transmission. The actual neurochemical mechanism is unknown, but CMI's relatively selective capacity to inhibit the reuptake of serotonin (5-HT) as compared to norepinephrine (NE) may be important.

Pharmacokinetics

Absorption/Bioavailability: CMI from Anafranil capsules is as bioavailable as CMI from a solution. The bioavailability of CMI from capsules is not significantly affected by food.

In a dose proportionality study involving multiple CMI doses, steady-state plasma concentrations (C_{ss}) and area-under-plasma-concentration-time curves (AUC) of CMI and CMI's major active metabolite, desmethylclomipramine (DMI), were not proportional to dose over the ranges evaluated, i.e., between 25-100 mg/day and between 25-150 mg/day, although C_{ss} and AUC are approximately linearly related to dose between 100-150 mg/day. The relationship between dose and CMI/DMI concentrations at higher daily doses has not been systematically assessed, but if there is significant dose dependency at doses above 150 mg/day, there is the potential for dramatically higher C_{ss} and AUC even for patients dosed within the recommended range. This may pose a potential risk to some patients (see WARNINGS and PRECAUTIONS, Drug Interactions).

After a single 50-mg oral dose, maximum plasma concentrations of CMI occur within 2-6 hours (mean, 4.7 hr) and range from 56 ng/ml to 154 ng/ml (mean, 92 ng/ml). After multiple daily doses of 150 mg of Anafranil, steady-state maximum plasma concentrations range from 94 ng/ml to 339 ng/ml (mean, 218 ng/ml) for CMI and from 134 ng/ml to 532 ng/ml (mean, 274 ng/ml) for DMI. No pharmacokinetic information is available for doses ranging from 150 mg/day to 250 mg/day, the maximum recommended daily dose.

Distribution: CMI distributes into cerebrospinal fluid (CSF) and brain and into breast milk. DMI also distributes into CSF, with a mean CSF/plasma ratio of 2.6. The protein binding of CMI is approximately 97%, principally to albumin, and is independent of CMI concentration. The interaction between CMI and other highly protein-bound drugs has not been fully evaluated, but may be important (see PRECAUTIONS, Drug Interactions).

Metabolism: CMI is extensively biotransformed to DMI and other metabolites and their glucuronide conjugates. DMI is pharmacologically active, but its effects on OCD behaviors are unknown. These metabolites are excreted in urine and feces, following biliary elimination. After a 25-mg radiolabeled dose of CMI in two subjects, 60% and 51%, respectively, of the dose were recovered in the urine and 32% and 24%, respectively, in feces. In the same study, the combined urinary recoveries of CMI and DMI were only about 0.8-1.3% of the dose administered. CMI does not induce drug-metabolizing enzymes, as measured by antipyrine half-life.

Elimination: Evidence that the C_{ss} and AUC for CMI and DMI may increase disproportionately with increasing oral doses suggests that the metabolism of CMI and DMI may be capacity limited. This fact must be considered in assessing the estimates of the pharmacokinetic parameters presented below, as these were obtained in individuals exposed to doses of 150 mg. If the pharmacokinetics of CMI and DMI are nonlinear at doses above 150 mg, their elimination half-lives may be considerably lengthened at doses near the upper end of the recommended dosing range (i.e., 200 mg/day to 250 mg/day). Consequently, CMI and DMI may accumulate, and this accumulation may increase the incidence of any dose- or plasma-concentration-dependent adverse reactions, in particular seizures (see WARNINGS).

After a 150-mg dose, the half-life of CMI ranges from 19 hours to 37 hours (mean, 32 hr) and that of DMI ranges from 54 hours to 77 hours (mean, 69 hr). Steady-state levels after multiple dosing are typically reached within 7-14 days for CMI. Plasma concentrations of the metabolite exceed the parent drug on multiple dosing. After multiple dosing with 150 mg/day, the accumulation factor for CMI is approximately 2.5 and for DMI is 4.6. Importantly, it may take two weeks or longer to achieve this extent of accumulation at constant dosing because of the relatively long elimination half-lives of CMI and DMI (see DOSAGE AND ADMINISTRATION). The effects of hepatic and renal impairment on the disposition of Anafranil have not been determined.

Pharmacokinetic Interactions: Coadministration of haloperidol with CMI increases plasma concentrations of CMI. Coadministration of CMI with phenobarbital increases plasma concentrations of phenobarbital (see PRECAUTIONS, Drug Interactions). Younger subjects (18-40 years of age) tolerated CMI better and had significantly lower steady-state plasma concentrations, compared with subjects over 65 years of age. Children under 15 years of age had significantly lower plasma concentration/dose ratios, compared with adults. Plasma concentrations of CMI were significantly lower in smokers than in nonsmokers.

INDICATIONS AND USAGE

Anafranil is indicated for the treatment of obsessions and compulsions in patients with Obsessive-Compulsive Disorder (OCD). The obsessions or compulsions must cause marked distress, be time-consuming, or significantly interfere with social or occupational functioning, in order to meet the DSM-III-R (circa 1989) diagnosis of OCD.

Obsessions are recurrent, persistent ideas, thoughts, images, or impulses that are ego-dystonic. Compulsions are repetitive, purposeful, and intentional behaviors performed in response to an obsession or in a stereotyped fashion, and are recognized by the person as excessive or unreasonable.

The effectiveness of Anafranil for the treatment of OCD was demonstrated in multicenter, placebo-controlled, parallel-group studies, including two 10-week studies in adults and one 8-week study in children and adolescents 10-17 years of age. Patients in all studies had moderate-to-severe OCD (DSM-III), with mean baseline ratings on the Yale-Brown Obsessive Compulsive Scale (YBOCS) ranging from 26 to 28 and a mean baseline rating of 10 on the NIMH Clinical Global Obsessive Compulsive Scale (NIMH-OC). Patients taking CMI experienced a mean reduction of approximately 10 on the YBOCS, representing an average improvement on this scale of 35% to 42% among adults and 37% among children and adolescents. CMI treated patients experienced a 3.5 unit decrement on the NIMH-OC. Patients on placebo showed no important clinical response on either scale. The maximum dose was 250 mg/day for most adults and 3 mg/kg/day (up to 200 mg) for all children and adolescents.

The effectiveness of Anafranil for long-term use (i.e., for more than 10 weeks) has not been systematically evaluated in placebo-controlled trials. The physician who elects to use Anafranil for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

Anafranil is contraindicated in patients with a history of hypersensitivity to Anafranil or other tricyclic antidepressants.

Anafranil should not be given in combination, or within 14 days before or after treatment, with a monoamine oxidase (MAO) inhibitor. Hyperpyretic crisis, seizures, coma, and death have been reported in patients receiving such combinations.

Anafranil is contraindicated during the acute recovery period after a myocardial infarction.

WARNINGS

Seizures

During premarket evaluation, seizure was identified as the most significant risk of Anafranil use.

The observed cumulative incidence of seizures among patients exposed to Anafranil at doses up to 300 mg/day was 0.64% at 90 days, 1.12% at 180 days, and 1.45% at 365 days. The cumulative rates cited correct the crude rate (i.e., 0.7%, 25/3519) for the variable duration of exposure times among the patients who participated in the development program.

Although dose appears to be a predictor of seizure, there is a confounding of dose and duration of exposure, making it difficult to assess independently the effect of either factor alone. The ability to predict the occurrence of seizures in subjects exposed to doses of CMI greater than 250 mg is limited, given that the plasma concentration of CMI may be dose-dependent and may vary among subjects given the same dose. Nevertheless, prescribers are advised to limit the daily dose to a maximum of 250 mg in adults and 3 mg/kg (or 200 mg) in children and adolescents (see DOSAGE AND ADMINISTRATION).

Rare reports of fatalities in association with seizures have been recorded by foreign post-marketing surveillance systems over the 20 years of Anafranil's nondomestic marketing. In some of these cases, Anafranil had been administered with other epileptogenic agents; in others, the patients involved had possibly predisposing medical conditions.

Caution should be used in administering Anafranil to patients with a history of seizures or other predisposing factors, e.g., brain damage of varying etiology, alcoholism, and concomitant use with other drugs that lower the seizure threshold.

Physicians should discuss with patients the risk of taking Anafranil while engaging in activities in which sudden loss of consciousness could result in serious injury to the patient or others, e.g., the operation of complex machinery, driving, swimming, climbing.

PRECAUTIONS

General

Suicide: Since depression is a commonly associated feature of OCD, the risk of suicide must be considered. Prescriptions for Anafranil should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

Cardiovascular Effects: Modest orthostatic decreases in blood pressure and modest tachycardia were each seen in approximately 20% of patients taking Anafranil in clinical trials; but patients were frequently asymptomatic. Among approximately 1400 patients treated with CMI in the premarketing experience who had ECGs, 1.5% developed abnormalities during treatment, compared with 3.1% of patients receiving active control drugs and 0.7% of patients receiving placebo. The most common ECG changes were PVCs, ST-T wave changes, and intraventricular conduction abnormalities. These changes were rarely associated with significant clinical symptoms. Nevertheless, caution is necessary in treating patients with known cardiovascular disease, and gradual dose titration is recommended.

Psychosis, Confusion, And Other Neuropsychiatric Phenomena: Patients treated with Anafranil have been reported to show a variety of neuropsychiatric signs and symptoms including delusions, hallucinations, psychotic episodes, confusion, and paranoia. Because of the uncontrolled nature of many of the studies, it is impossible to provide a precise estimate of the extent of risk imposed by treatment with Anafranil. As with tricyclic antidepressants to which it is closely related, Anafranil may precipitate an acute psychotic episode in patients with unrecognized schizophrenia.

Mania/Hypomania: During premarketing testing of Anafranil in patients with affective disorder, hypomania or mania was precipitated in several patients. Activation of mania or hypomania has also been reported in a small proportion of patients with affective disorder treated with marketed tricyclic antidepressants, which are closely related to Anafranil.

Hepatic Changes: During premarketing testing, Anafranil was occasionally associated with elevations in SGOT and SGPT (pooled incidence of approximately 1% and 3%, respectively) of potential clinical importance (i.e., values greater than 3 times the upper limit of normal). In the vast majority of instances these enzyme increases were not associated with other clinical findings suggestive of hepatic injury; moreover, none were jaundiced. Rare reports of more severe liver injury, some fatal, have been recorded in foreign post-marketing experience. Caution is indicated in treating patients with known liver disease, and periodic monitoring of hepatic enzyme levels is recommended in such patients.

Hematologic Changes: Although no instances of severe hematologic toxicity were seen in the premarketing experience with Anafranil, there have been post-marketing reports of leukopenia, agranulocytosis, thrombocytopenia, anemia, and pancytopenia in association with Anafranil use. As is the case with tricyclic antidepressants to which Anafranil is closely related, leukocyte and differential blood counts should be obtained in patients who develop fever and sore throat during treatment with Anafranil.

Central Nervous System: More than 30 cases of hyperthermia have been recorded by nondomestic post-marketing surveillance systems. Most cases occurred when Anafranil was used in combination with other drugs when Anafranil and a neuroleptic were used concomitantly, the cases were sometimes considered to be examples of a neuroleptic malignant syndrome.

Sexual Dysfunction: The rate of sexual dysfunction in male patients with OCD who were treated with Anafranil in the premarketing experience was markedly increased compared with placebo controls (i.e., 42% experienced ejaculatory failure and 20% experienced impotence, compared with 2.0% and 2.6%, respectively, in the placebo group). Approximately 85% of males with sexual dysfunction chose to continue treatment.

Weight Changes: In controlled studies of OCD, weight gain was reported in 18% of patients receiving Anafranil, compared with 1% of patients receiving placebo. In these studies, 28% of patients receiving Anafranil had a weight gain of at least 7% of their initial body weight, compared with 4% of patients receiving placebo. Several patients had weight gains in excess of 25% of their initial body weight. Conversely, 5% of patients receiving Anafranil and 1% receiving placebo had weight losses of at least 7% of their initial body weight.

Electroconvulsive Therapy: As with closely related tricyclic antidepressants, concurrent administration of Anafranil with electroconvulsive therapy may increase the risks; such treatment should be limited to those patients for whom it is essential, since there is limited clinical experience.

Surgery: Prior to elective surgery with general anesthetics, therapy with Anafranil should be discontinued for as long as is clinically feasible, and the anesthetist should be advised.

Use in Concomitant Illness: As with closely related tricyclic antidepressants, Anafranil should be used with caution in the following:

1. Hyperthyroid patients or patients receiving thyroid medication, because of the possibility of cardiac toxicity.
2. Patients with increased intraocular pressure, a history of narrow-angle glaucoma, or urinary retention, because of the anticholinergic properties of the drug.
3. Patients with tumors of the adrenal medulla (e.g., pheochromocytoma, neuroblastoma) in whom the drug may provoke hypertensive crises.
4. Patients with significantly impaired renal function.

Withdrawal Symptoms: A variety of withdrawal symptoms have been reported in association with abrupt discontinuation of Anafranil, including dizziness, nausea, vomiting, headache, malaise, sleep disturbance, hyperthermia, and irritability. In addition, such patients may experience a worsening of psychiatric status. While the withdrawal effects of Anafranil have not been systematically evaluated in controlled trials, they are well known with closely related tricyclic antidepressants, and it is recommended that the dosage be tapered gradually and the patient monitored carefully during discontinuation (see DRUG ABUSE AND DEPENDENCE).

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe Anafranil:

1. The risk of seizure (see WARNINGS).
2. The relatively high incidence of sexual dysfunction among males (see PRECAUTIONS, Sexual Dysfunction).
3. Since Anafranil may impair the mental and/or physical abilities required for t performance of complex tasks, and since Anafranil is associated with a risk of seizures, patients should be cautioned about the performance of complex ar hazardous tasks (see WARNINGS).
4. Patients should be cautioned about using alcohol, barbiturates, or other CN depressants concurrently, since Anafranil may exaggerate their response to these drugs.
5. Patients should notify their physician if they become pregnant or intend to become pregnant during therapy.
6. Patients should notify their physician if they are breast-feeding.

Drug Interactions

The risks of using Anafranil in combination with other drugs have not been systematically evaluated. Given the primary CNS effects of Anafranil, caution is advised in using it concomitantly with other CNS-active drugs (see PRECAUTIONS, Information for Patients). Anafranil should *not* be used with MAO inhibitors (see CONTRAINDICATIONS).

Close supervision and careful adjustment of dosage are required when Anafranil is administered with anticholinergic or sympathomimetic drugs.

Several tricyclic antidepressants have been reported to block the pharmacologic effects of guanethidine, clonidine, or similar agents, and such an effect ma be anticipated with CMI because of its structural similarity to other tricyclic antidepressants.

The plasma concentration of CMI has been reported to be increased by the concomitant administration of haloperidol; plasma levels of several closely related tricyclic antidepressants have been reported to be increased by the concomitant administration of either methylphenidate, cimetidine, or fluoxetine and such an effect may be anticipated with CMI as well. Administration of C has been reported to increase the plasma levels of phenobarbital, if given concomitantly (see CLINICAL PHARMACOLOGY, Pharmacokinetic Interaction

Because Anafranil is highly bound to serum protein, the administration of Anafranil to patients taking other drugs that are highly bound to protein (e.g., warfarin, digoxin) may cause an increase in plasma concentrations of these drugs, potentially resulting in adverse effects. Conversely, adverse effects may result from displacement of protein-bound Anafranil by other highly bound drug (see CLINICAL PHARMACOLOGY, Distribution).

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year bioassay, no clear evidence of carcinogenicity was found in rats give doses 20 times the maximum daily human dose. Three out of 235 treated rats h a rare tumor (hemangioendothelioma); it is unknown if these neoplasms are compound related.

In reproduction studies, no effects on fertility were found in rats given doses approximately 5 times the maximum daily human dose.

Pregnancy Category C

No teratogenic effects were observed in studies performed in rats and mice at doses up to 20 times the maximum daily human dose. Slight nonspecific fetoto effects were seen in the offspring of pregnant mice given doses 10 times the maximum daily human dose. Slight nonspecific embryotoxicity was observed in rats given doses 5-10 times the maximum daily human dose.

There are no adequate or well-controlled studies in pregnant women. Withdrawal symptoms, including jitteriness, tremor, and seizures, have been reported in neonates whose mothers had taken Anafranil until delivery. Anafran should be used during pregnancy only if the potential benefit justifies the potent risk to the fetus.

Nursing Mothers

Anafranil has been found in human milk. Because of the potential for adverse reactions, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the moth

Pediatric Use

In a controlled clinical trial in children and adolescents (10-17 years of age), 46 outpatients received Anafranil for up to 8 weeks. In addition, 150 adolescent patients have received Anafranil in open-label protocols for periods of several months to several years. Of the 196 adolescents studied, 50 were 13 years of ag or less and 146 were 14-17 years of age. While the adverse reaction profile in thi age group (see ADVERSE REACTIONS) is similar to that in adults, it is unknown what, if any, effects long-term treatment with Anafranil may have on the grow and development of children.

The safety and effectiveness in children below the age of 10 have not been established. Therefore, specific recommendations cannot be made for the use Anafranil in children under the age of 10.

Use in Elderly

Anafranil has not been systematically studied in older patients; but 152 patients least 60 years of age participating in U.S. clinical trials received Anafranil for periods of several months to several years. No unusual age-related adverse events have been identified in this elderly population, but these data are insufficient to rule out possible age-related differences, particularly in elderly patients who have concomitant systemic illnesses or who are receiving othe drugs concomitantly.

ADVERSE REACTIONS

Commonly Observed

The most commonly observed adverse events associated with the use of Anafranil and not seen at an equivalent incidence among placebo-treated patients were gastrointestinal complaints, including dry mouth, constipation, nausea, dyspepsia, and anorexia; nervous system complaints, including somnolence, tremor, dizziness, nervousness, and myoclonus; genitourinary complaints, including changed libido, ejaculatory failure, impotence, and micturition disorder; and other miscellaneous complaints, including fatigue, sweating, increased appetite, weight gain, and visual changes.

Leading to Discontinuation of Treatment

Approximately 20% of 3616 patients who received Anafranil in U.S. premarketin clinical trials discontinued treatment because of an adverse event. Approximate one-half of the patients who discontinued (9% of the total) had multiple complaints, none of which could be classified as primary. Where a primary reason fo discontinuation could be identified, most patients discontinued because of nervous system complaints (5.4%), primarily somnolence. The second-most-frequent reason for discontinuation was digestive system complaints (1.3%), primarily vomiting and nausea.

Incidence in Controlled Clinical Trials

The following table enumerates adverse events that occurred at an incidence of 1% or greater among patients with OCD who received Anafranil in adult or pediatric placebo-controlled clinical trials. The frequencies were obtained from pooled data of clinical trials involving either adults receiving Anafranil (N = 322) placebo (N = 319) or children treated with Anafranil (N = 46) or placebo (N = 44). The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice, in which patien characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, provide the physician with a basis for estimating the relative contribution of drug and nondrug factors to the incidence of side effects in the populations studied.

Incidence of Treatment-Emergent Adverse Experience in Placebo-Controlled Clinical Trials
(Percentage of Patients Reporting)

	Adults		Children and Adolescents	
Body System/ Adverse Event*	**Anafranil (N=322)**	**Placebo (N=319)**	**Anafranil (N=46)**	**Place (N=4**
Nervous System				
Somnolence	54	16	46	11
Tremor	54	2	33	2
Dizziness	54	14	41	14
Headache	52	41	28	34
Insomnia	25	15	11	7

Anafranil® clomipramine hydrochloride

Body System/ Adverse Event *	Adults		Children and Adolescents	
	Anafranil (N=322)	Placebo (N=319)	Anafranil (N=46)	Placebo (N=44)
Libido change	21	3	—	—
Nervousness	18	2	4	2
Myoclonus	13	—	2	—
Increased appetite	11	2	—	2
Paresthesia	9	3	2	2
Memory impairment	9	1	7	2
Anxiety	9	4	2	—
Twitching	7	1	4	5
Impaired concentration	5	2	—	—
Depression	5	1	—	—
Hypertonia	4	1	2	—
Sleep disorder	4	—	9	5
Psychosomatic disorder	3	—	—	—
Yawning	3	—	—	—
Confusion	3	—	2	—
Speech disorder	3	—	—	—
Abnormal dreaming	3	—	—	2
Agitation	3	—	—	—
Migraine	3	—	—	—
Depersonalization	2	—	2	—
Irritability	2	2	2	—
Emotional lability	2	—	—	2
Panic reaction	1	—	2	—
Aggressive reaction	—	—	2	—
Paresis	—	—	2	—
Skin and Appendages				
Increased sweating	29	3	9	—
Rash	8	1	4	2
Pruritus	6	—	2	2
Dermatitis	2	—	—	2
Acne	2	2	—	5
Dry skin	2	—	—	5
Urticaria	1	—	—	—
Abnormal skin odor	—	—	2	—
Digestive System				
Dry mouth	84	17	63	16
Constipation	47	11	22	9
Nausea	33	14	9	11
Dyspepsia	22	10	13	2
Diarrhea	13	9	7	5
Anorexia	12	—	22	2
Abdominal pain	11	9	13	16
Vomiting	7	2	7	—
Flatulence	6	3	—	2
Tooth disorder	5	—	—	—
Gastrointestinal disorder	2	—	—	2
Dysphagia	2	—	—	—
Esophagitis	1	—	—	—
Eructation	—	—	2	2
Ulcerative stomatitis	—	—	2	—
Body as a Whole				
Fatigue	39	18	35	9
Weight increase	18	1	2	—
Flushing	8	—	7	—
Hot flushes	5	—	2	—
Chest pain	4	4	7	—
Fever	4	—	2	7
Allergy	3	3	7	5
Pain	3	2	4	2
Local edema	2	4	—	—
Chills	2	1	—	—
Weight decrease	—	—	7	—
Otitis media	—	—	4	5
Asthenia	—	—	2	—
Halitosis	—	—	2	—
Cardiovascular System				
Postural hypotension	6	—	4	—
Palpitation	4	2	4	—
Tachycardia	4	—	2	—
Syncope	—	—	2	—
Respiratory System				
Pharyngitis	14	9	—	5
Rhinitis	12	10	7	9
Sinusitis	6	4	2	5
Coughing	6	6	4	5
Bronchospasm	2	—	7	2
Epistaxis	2	—	—	2
Dyspnea	—	—	2	—
Laryngitis	—	1	2	—
Urogenital System				
Male and Female Patients Combined				
Micturition disorder	14	2	4	2
Urinary tract infection	6	1	—	—
Micturition frequency	5	3	—	—
Urinary retention	2	—	7	—
Dysuria	2	2	—	—
Cystitis	2	—	—	—
Female Patients Only	(N = 182)	(N = 167)	(N = 10)	(N = 21)
Dysmenorrhea	12	14	10	10
Lactation (nonpuerperal)	4	—	—	—
Menstrual disorder	4	2	—	—
Vaginitis	2	—	—	—
Leukorrhea	2	—	—	—
Breast enlargement	2	—	—	—
Breast pain	1	—	—	—
Amenorrhea	1	—	—	—
Male Patients Only	(N = 140)	(N = 152)	(N = 36)	(N = 23)
Ejaculation failure	42	2	6	—
Impotence	20	3	—	—
Special Senses				
Abnormal vision	18	4	7	2
Taste perversion	8	—	4	—
Tinnitus	6	—	4	—
Abnormal lacrimation	3	2	—	—
Mydriasis	2	—	—	—
Conjunctivitis	1	—	—	—
Anisocoria	—	—	2	—
Blepharospasm	—	—	2	—
Ocular allergy	—	—	2	—
Vestibular disorder	—	—	2	2
Musculoskeletal				
Myalgia	13	9	—	—
Back pain	6	6	—	—
Arthralgia	3	5	—	—
Muscle weakness	1	—	2	—
Hemic and Lymphatic				
Purpura	3	—	—	—
Anemia	—	—	2	2
Metabolic and Nutritional				
Thirst	2	2	—	2

*Events reported by at least 1% of Anafranil patients are included

Other Events Observed During the Premarketing Evaluation of Anafranil

During clinical testing in the U.S., multiple doses of Anafranil were administered to approximately 3600 subjects. Untoward events associated with this exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories.

In the tabulations that follow, a modified World Health Organization dictionary of terminology has been used to classify reported adverse events. The frequencies presented, therefore, represent the proportion of the 3525 individuals exposed to Anafranil who experienced an event of the type cited on at least one occasion while receiving Anafranil. All events are included except those already listed in the previous table, those reported in terms so general as to be uninformative, and those in which an association with the drug was remote. It is important to emphasize that although the events reported occurred during treatment with Anafranil, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in less than 1/1000 patients.

Body as a Whole: *Infrequent* — general edema, increased susceptibility to infection, malaise. *Rare* — dependent edema, withdrawal syndrome.

Cardiovascular System: *Infrequent* — abnormal ECG, arrhythmia, bradycardia, cardiac arrest, extrasystoles, pallor. *Rare* — aneurysm, atrial flutter, bundle branch block, cardiac failure, cerebral hemorrhage, heart block, myocardial infarction, myocardial ischemia, peripheral ischemia, thrombophlebitis, vasospasm, ventricular tachycardia.

Digestive System: *Infrequent* — abnormal hepatic function, blood in stool, colitis, duodenitis, gastric ulcer, gastritis, gastroesophageal reflux, gingivitis, glossitis, hemorrhoids, hepatitis, increased saliva, irritable bowel syndrome, peptic ulcer, rectal hemorrhage, tongue ulceration, tooth caries. *Rare* — cheilitis, chronic enteritis, discolored feces, gastric dilatation, gingival bleeding, hiccup, intestinal obstruction, oral/pharyngeal edema, paralytic ileus, salivary gland enlargement.

Endocrine System: *Infrequent* — hypothyroidism. *Rare* — goiter, gynecomastia, hyperthyroidism.

Hemic and Lymphatic System: *Infrequent* — lymphadenopathy. *Rare* — leukemoid reaction, lymphoma-like disorder, marrow depression.

Metabolic and Nutritional Disorder: *Infrequent* — dehydration, diabetes mellitus, gout, hypercholesterolemia, hyperglycemia, hyperuricemia, hypokalemia. *Rare* — fat intolerance, glycosuria.

Musculoskeletal System: *Infrequent* — arthrosis. *Rare* — dystonia, exostosis, lupus erythematosus rash, bruising, myopathy, myositis, polyarteritis nodosa, torticollis.

Nervous System: *Frequent* — abnormal thinking, vertigo. *Infrequent* — abnormal coordination, abnormal EEG, abnormal gait, apathy, ataxia, coma, convulsions, delirium, delusion, dyskinesia, dysphonia, encephalopathy, euphoria, extrapyramidal disorder, hallucinations, hostility, hyperkinesia, hypnagogic hallucinations, hypokinesia, leg cramps, manic reaction, neuralgia, paranoia, phobic disorder, psychosis, sensory disturbance, somnambulism, stimulation, suicidal ideation, suicide attempt, teeth-grinding. *Rare* — anticholinergic syndrome, aphasia, apraxia, catalepsy, cholinergic syndrome, choreoathetosis, generalized spasm, hemiparesis, hyperesthesia, hyperreflexia, hypoesthesia, illusion, impaired impulse control, indecisiveness, mutism, neuropathy, nystagmus, oculogyric crisis, oculomotor nerve paralysis, schizophrenic reaction, stupor, suicide.

Respiratory System: *Infrequent* — bronchitis, hyperventilation, increased sputum, pneumonia. *Rare* — cyanosis, hemoptysis, hypoventilation, laryngismus.

Skin and Appendages: *Infrequent* — alopecia, cellulitis, cyst, eczema, erythematous rash, genital pruritus, maculopapular rash, photosensitivity reaction, psoriasis, pustular rash, skin discoloration. *Rare* — chloasma, folliculitis, hypertrichosis, piloerection, seborrhea, skin hypertrophy, skin ulceration.

Special Senses: *Infrequent* — abnormal accommodation, deafness, diplopia, earache, eye pain, foreign body sensation, hyperacusis, parosmia, photophobia, scleritis, taste loss. *Rare* — blepharitis, chromatopsia, conjunctival hemorrhage, exophthalmos, glaucoma, keratitis, labyrinth disorder, night blindness, retinal disorder, strabismus, visual field defect.

Urogenital System: *Infrequent* — endometriosis, epididymitis, hematuria, nocturia, oliguria, ovarian cyst, perineal pain, polyuria, prostatic disorder, renal calculus, renal pain, testis disorder, urethral disorder, urinary incontinence, uterine hemorrhage, vaginal hemorrhage. *Rare* — albuminuria, anorgasmy, breast engorgement, breast fibroadenosis, cervical dysplasia, endometrial hyperplasia, premature ejaculation, pyelonephritis, pyuria, renal cyst, uterine inflammation, vulvar disorder.

DRUG ABUSE AND DEPENDENCE

Anafranil has not been systematically studied in animals or humans for its potential for abuse, tolerance, or physical dependence. While a variety of withdrawal symptoms have been described in association with Anafranil discontinuation (see PRECAUTIONS, Withdrawal Symptoms), there is no evidence for drug-seeking behavior, except for a single report of potential Anafranil abuse by a patient with a history of dependence on codeine, benzodiazepines, and multiple psychoactive drugs. The patient received Anafranil for depression and panic attacks and appeared to become dependent after hospital discharge.

Despite the lack of evidence suggesting an abuse liability for Anafranil in foreign marketing, it is not possible to predict the extent to which Anafranil might be misused or abused once marketed in the U.S. Consequently, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely.

OVERDOSAGE

Human Experience

In U.S. clinical trials, 2 deaths occurred in 12 reported cases of acute overdosage with Anafranil either alone or in combination with other drugs. One death involved a patient suspected of ingesting a dose of 7000 mg. The second death involved a patient suspected of ingesting a dose of 5750 mg. The 10 nonfatal cases involved doses of up to 5000 mg, accompanied by plasma levels of up to 1010 ng/ml. All 10 patients completely recovered. Among reports from other countries of Anafranil overdose, the lowest dose associated with a fatality was 750 mg. Based upon post-marketing reports in the United Kingdom, CMI's lethality in overdose is considered to be similar to that reported for closely related tricyclic compounds marketed as antidepressants.

Signs and Symptoms

Signs and symptoms vary in severity depending upon factors such as the amount of drug absorbed, the age of the patient, and the time elapsed since drug ingestion. Blood and urine levels of Anafranil may not reflect the severity of poisoning: they have chiefly a qualitative rather than quantitative value, and they are unreliable indicators in the clinical management of the patient. The first signs and symptoms of poisoning with tricyclic antidepressants are generally severe anticholinergic reactions. CNS abnormalities may include drowsiness, stupor, coma, ataxia, restlessness, agitation, delirium, severe perspiration, hyperactive reflexes, muscle rigidity, athetoid and choreiform movements, and convulsions. Cardiac abnormalities may include arrhythmia, tachycardia, ECG evidence of impaired conduction, and signs of congestive heart failure, and in very rare cases, cardiac arrest. Respiratory depression, cyanosis, hypotension,shock, vomiting, hyperpyrexia, mydriasis, oliguria or anuria, and diaphoresis may also be present.

Treatment

The recommended treatment for tricyclic overdose may change periodically. Therefore, it is recommended that the physician contact a poison control center for current information on treatment.

Because CNS involvement, respiratory depression, and cardiac arrhythmia can occur suddenly, hospitalization and close observation are necessary, even when the amount ingested is thought to be small or the initial degree of intoxication appears slight or moderate. All patients with ECG abnormalities should have continuous cardiac monitoring for at least 72 hours and be closely observed until well after the cardiac status has returned to normal; relapses may occur after apparent recovery. The slow intravenous administration of physostigmine salicylate has been reported to reverse the cardiovascular and CNS anticholinergic manifestations of tricyclic overdosage; however, it should not be used routinely, since it may induce seizures and cholinergic crises and there is persisting debate about its net utility.

In the alert patient, the stomach should be emptied promptly by induced emesis followed by lavage. In the obtunded patient, the airway should be secured with a cuffed endotracheal tube before beginning lavage (do not induce emesis). Lavage should be continued for 24 hours or longer, depending on the apparent severity of intoxication. Normal or half-normal saline should be used to avoid water intoxication, especially in children. Instillation of activated charcoal slurry may help reduce absorption of CMI.

External stimulation should be minimized to reduce the tendency for convulsions, and anticonvulsants may be necessary. If MAO inhibitors have been taken recently, barbiturates should not be used. Adequate respiratory exchange should be maintained, including intubation and artificial respiration, if necessary. Respiratory stimulants should not be used.

In severe hypotension or shock, the patient should be placed in an appropriate position and given a plasma expander, dopamine, or dobutamine by intravenous drip. The use of corticosteroids in shock is controversial and may be contraindicated in cases of overdosage with tricyclic antidepressants. Digitalis may increase conduction abnormalities and further irritate an already sensitized myocardium. If congestive heart failure necessitates rapid digitalization, particular care must be exercised. Hyperpyrexia should be controlled by whatever external means are available, including ice packs and cooling sponge baths, if necessary. Hemodialysis, peritoneal dialysis, exchange transfusions, and forced diuresis have generally been reported as ineffective because of the rapid fixation of Anafranil in tissues.

DOSAGE AND ADMINISTRATION

The treatment regimens described below are based on those used in controlled clinical trials of Anafranil in 520 adults, and 91 children and adolescents with OCD. During initial titration, Anafranil should be given in divided doses with meals to reduce gastrointestinal side effects. The goal of this initial titration phase is to minimize side effects by permitting tolerance to side effects to develop or allowing the patient time to adapt if tolerance does not develop.

Because both CMI and its active metabolite, DMI, have long elimination half-lives, the prescriber should take into consideration the fact that steady-state plasma levels may not be achieved until 2-3 weeks after dosage change (see CLINICAL PHARMACOLOGY). Therefore, after initial titration, it may be appropriate to wait 2-3 weeks between further dosage adjustments.

Initial Treatment/Dose Adjustment (Adults)

Treatment with Anafranil should be initiated at a dosage of 25 mg daily and gradually increased, as tolerated, to approximately 100 mg during the first 2 weeks. During initial titration, Anafranil should be given in divided doses with meals to reduce gastrointestinal side effects. Thereafter, the dosage may be increased gradually over the next several weeks, up to a maximum of 250 mg daily. After titration, the total daily dose may be given once daily at bedtime to minimize daytime sedation.

Initial Treatment/Dose Adjustment (Children and Adolescents)

As with adults, the starting dose is 25 mg daily and should be gradually increased (also given in divided doses with meals to reduce gastrointestinal side effects) during the first 2 weeks, as tolerated, up to a daily maximum of 3 mg/kg or 100 mg, whichever is smaller. Thereafter, the dosage may be increased gradually over the next several weeks up to a daily maximum of 3 mg/kg or 200 mg, whichever is smaller (see PRECAUTIONS, Pediatric Use). As with adults, after titration, the total daily dose may be given once daily at bedtime to minimize daytime sedation.

Maintenance/Continuation Treatment (Adults, Children, and Adolescents)

While there are no systematic studies that answer the question of how long to continue Anafranil, OCD is a chronic condition and it is reasonable to consider continuation for a responding patient. Although the efficacy of Anafranil after 10 weeks has not been documented in controlled trials, patients have been continued in therapy under double-blind conditions for up to 1 year without loss of benefit. However, dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for treatment. During maintenance, the total daily dose may be given once daily at bedtime.

HOW SUPPLIED

Capsules 25 mg — ivory/melon yellow (imprinted ANAFRANIL 25 mg)
  Bottles of 100 .... NDC 0083-0115-30
  Unit Dose (blister pack)
    Box of 100 (strips of 10) .... NDC 0083-0115-32
Capsules 50 mg — ivory/aqua blue (imprinted ANAFRANIL 50 mg)
  Bottles of 100 .... NDC 0083-0116-30
  Unit Dose (blister pack)
    Box of 100 (strips of 10) .... NDC 0083-0116-32
Capsules 75 mg — ivory/yellow (imprinted ANAFRANIL 75 mg)
  Bottles of 100 .... NDC 0083-0117-30
  Unit Dose (blister pack)
    Box of 100 (strips of 10) .... NDC 0083-0117-32

Do not store above 86°F (30°C). Protect from moisture.

Dispense in tight container (USP).

ANIMAL TOXICOLOGY

Testicular and lung changes commonly associated with tricyclic compounds have been observed with Anafranil. In 1- and 2-year studies in rats, changes in the testes (atrophy, aspermatogenesis, and calcification) and drug-induced phospholipidosis in the lungs were observed at doses 4 times the maximum daily human dose. Testicular atrophy was also observed in a 1-year oral toxicity study in dogs at 10 times the maximum daily human dose.

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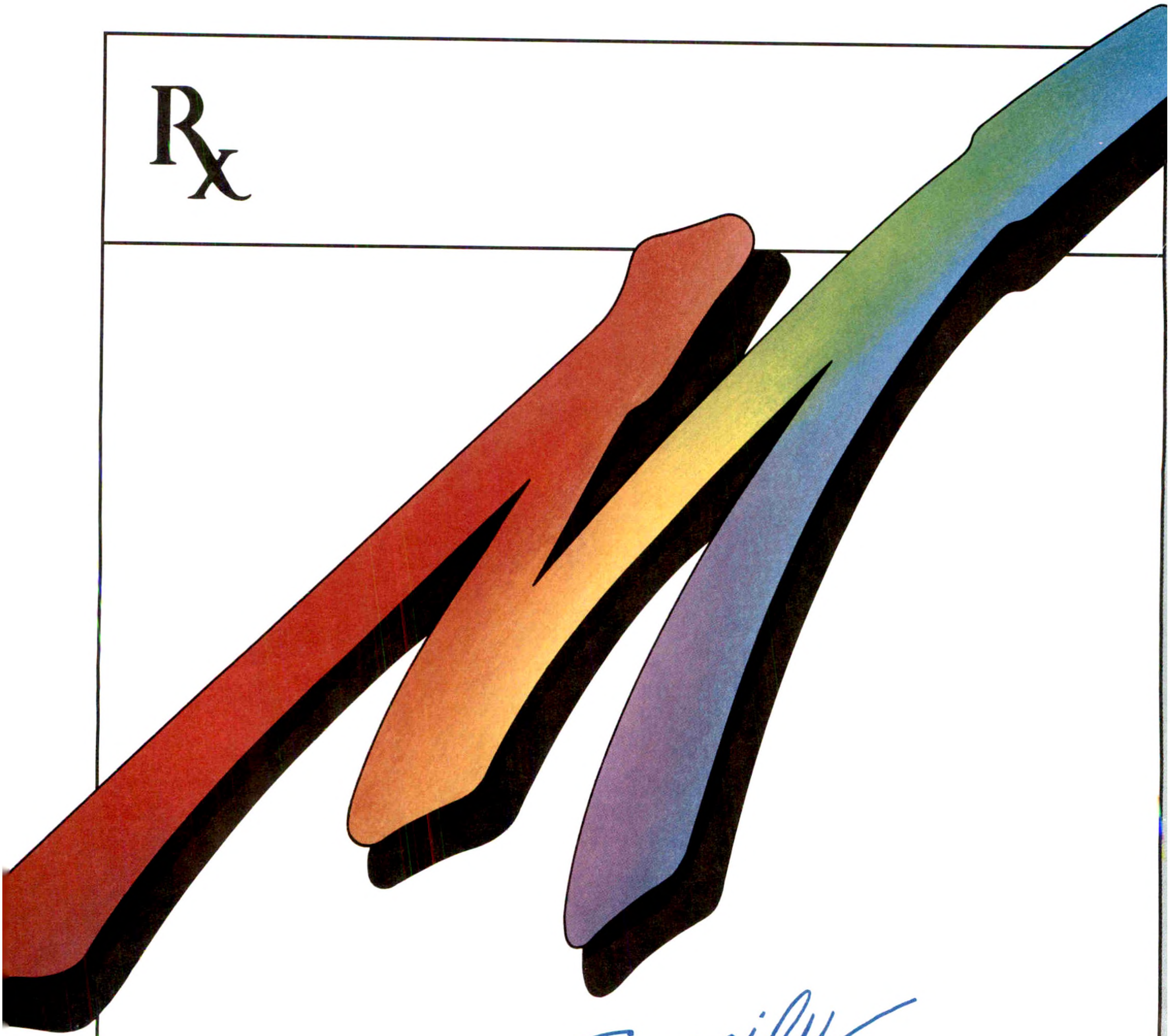

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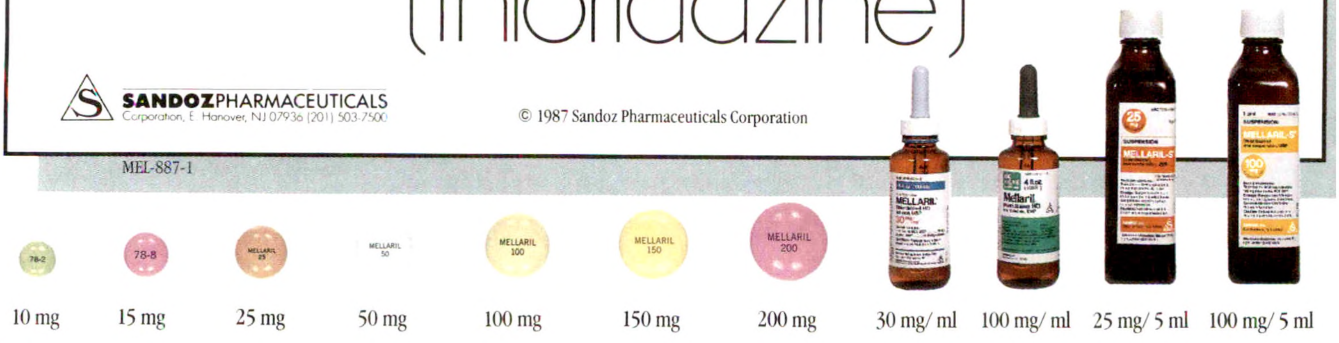

THE AMERICAN JOURNAL OF PSYCHIATRY
Special Article

The Déjà Vu Experience: Remembrance of Things Past?

Herman N. Sno, M.D., and Don H. Linszen, M.D.

The déjà vu experience is a common phenomenon, occurring in pathological as well as nonpathological conditions. It has been defined as any subjectively inappropriate impression of familiarity of a present experience with an undefined past. The authors discuss the epidemiologic data, clinical features, and etiology of the phenomenon of déjà vu. They also review the different hypotheses on the psychopathogenesis of the déjà vu experience and introduce an explanation based on the hologram as a mnestic model.

(Am J Psychiatry 1990; 147:1587–1595)

In *The Psychopathology of Everyday Life* (1) Freud wrote, "We must include in the category of the miraculous and the 'uncanny' the peculiar feeling we have, in certain moments and situations, of having had exactly the same experience once before or of having once before been in the same place, though our efforts never succeed in clearly remembering the previous occasion that announces itself in this way. . . . I know that the subject would merit the most exhaustive treatment."

Like the founder of classical psychoanalysis, many novelists and poets have also been fascinated by this "peculiar feeling." Frequent references have been made to descriptions of the déjà vu experience in *David Copperfield* (1849) by Charles Dickens, *"Childhood," "Boyhood," and "Youth"* (1852) by Leo Tolstoy, and *Remembrance of Things Past* (1919) by Marcel Proust. The déjà vu experience was also depicted by Sir Walter Scott in *Guy Mannering* (1815), by Leo Tolstoy in *War and Peace* (1859), by Goncharov in *Oblomov* (1859), and by Thomas Hardy in "A Pair of Blue Eyes" (1872). It has been described more recently by Joseph Heller in *Catch-22* (1955), by Isaac Bashevis Singer in "Jachid and Jechidah" (1961), and by Walker Percy in *The Last Gentleman* (1966). Other examples include the poems "To—(As When With Downcast Eyes)" (1832) and "The Two Voices" (1833) by Alfred Tennyson and "Sudden Light" (1854) by D.G. Rossetti and the songs "Where or When" (1937) by Rodgers and Hart and "Déjà Vu" (1970) by David Crosby. In Susan Seidelman's movie *Desperately Seeking Susan* (1985), the heroine has a déjà vu experience following a head trauma.

Centuries ago, St. Augustine (2) referred to the phenomenon as *falsae memoriae*. In 1828, Sir Walter Scott (3) spoke of "the sense of pre-existence." To our knowledge, it was the English physician Arthur Ladbroke Wigan (4) who was the first to focus psychiatric attention on what he called "the sentiment of pre-existence." The phenomenon has been described by various authors of differing nationalities using a multitude of alternative terms (see table 1).

In 1896 Arnaud (14) concluded that as long as there was not yet any certainty as to the etiology of the phenomenon, a pathogenetically neutral term such as "déjà vu" would be preferable. In his opinion, such terms as *fausse mémoire* and *paramnésie* erroneously suggested that it was solely a disturbance of memory. However, the term "déjà vu" gave rise to the notion that it was solely a disturbance of visual perception. The phenomenon has since become generally known and accepted in the English language as the déjà vu experience.

After defining the term déjà vu experience, we will

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TABLE 1. Alternative Terms for the Déjà Vu Experience

Country and Term	Year	Author
Britain		
Sentiment of pre-existence	1844	Wigan (4)
Reminiscence	1888	Jackson (5)
Sense of prescience	1895	Crichton-Browne (6)
Promnesia	1895	Myers (7)
Germany		
Empfindungsspiegelung	1859	Neumann (8)
Doppelwahrnehmungen	1868	Jensen (9)
Doppelvorstellungen	1871	Huppert (10)
Erinnerungstäuschungen	1873	Sander (11)
Identificerende Erinnerungsfälschung	1887	Kraepelin (12)
France		
Sensation du déjà vu	1876	Boirac (13)
Fausse mémoire	1880	Ribot (cited by Arnaud [14])
Paramnésie	1893	Lalande (15)
Illusion de déjà vu	1896	Arnaud (14)
Illusion de fausse reconnaissance	1898	Bernard-Leroy (16)
Sentiment de "déjà vu"	1905	Janet (17)
Souvenir du present	1908	Bergson (18)
United States		
Illusion of memory	1884	Osborn (19)
Identifying paramnesia	1889	Burnham (20)
Illusion of "the already seen"	1921	Gordon (21)
Illusion of familiarity	1954	Penfield and Jasper (22)

deal in this article with its epidemiology and clinical features. We will then discuss the etiology of the phenomenon as well as psychopathogenetic hypotheses and models.

DEFINITION

Déjà vu is French for "already seen." In everyday language, the term is often misused in the literal sense. When a man first approaches a woman, for example, instead of using the cliché "I feel like we have met before," he might say something like, "I feel like I am having a déjà vu." As proposed by Neppe (23, 24), the déjà vu experience is defined as "Any subjectively inappropriate impression of familiarity of a present experience with an undefined past" (24). The phenomenon can be regarded as the opposite of the *jamais vu* experience, in which there is an inappropriate absence of familiarity (*jamais vu* is French for "never seen").

The déjà vu experience must be differentiated from such phenomena as flashbacks, cryptomnesia, actualized precognition, and vivid memory. In the event of flashbacks, individuals may conceive themselves as actually being back in time or may see facets of their past lives before their eyes. There is no sense of familiarity involved. In the event of cryptomnesia, there is no comparison with the present but a sense of past ideas that are inappropriately unfamiliar. The term "actualized precognition" refers to the subjective impression that the present situation has been foretold. In a vivid memory, the past comes into focus, but there is nothing in the present that seems familiar (23).

EPIDEMIOLOGY

The déjà vu experience is a common phenomenon. It occurs not only in medical and psychiatric disorders but, as many of us know from our own experience, in nonpathological conditions as well.

The reported rates of the déjà vu experience vary from 30% to 96% (see table 2). This variation in rates is probably partially based on selective factors and the use of differing definitions of the déjà vu experience.

Most authors writing on déjà vu indicated a greater predilection at younger ages, but no striking gender differences were reported. There is less consensus as to the correlation with other demographic variables, such as education, socioeconomic status, and race. Some authors (15, 24, 26) found no significant correlation with these variables. Others (6, 29, 33), however, reported significant correlations with education and socioeconomic status.

CLINICAL FEATURES

In their descriptions of the clinical features of the déjà vu experience, most authors on the subject distinguished two varieties. Whether the differences between the two are qualitative or quantitative remains controversial. Many authors (29, 34, 35) assumed a qualitative difference, i.e., a nonpathological and a pathological form. In order to emphasize this difference, Berndt-Larsson (34) proposed, following Albès (36), that the nonpathological form be referred to as *déjà-éprouvé* and the pathological form as *fausse reconnaissance* or "reduplicating paramnesia." Arnaud (14), however, suggested a quantitative difference: a minor (*forme légère*) and a major (*forme grave*) form. He pointed out that the minor form may occur in pathological as well as in nonpathological conditions and that it is transient, it has a rapid onset and disappearance, and reality testing remains intact. The major form is clearly pathological and prolonged, and reality testing is persistently or recurrently impaired. The dispute as to whether there are qualitative or quantitative differences will not be settled here. Since the clinical features of the déjà vu experience are so universally similar and can be identical in pathological and nonpathological conditions, a qualitative difference would seem less likely. We tend to prefer Arnaud's distinction of minor and major forms.

Neppe's definition of the phenomenon (23, 24) epitomized the clinical features of the déjà vu experience in one sentence ("Any subjectively inappropriate impression of familiarity of a present experience, with an undefined past"). By the word "any," he indicated that it is an etiologically neutral phenomenon. He did not make any statement as to its duration. Most authors

TABLE 2. Déjà Vu Experiences Reported in the Literature

Author	Year	Group Studied	Sex of Subjects in Group	Subjects Who Experienced Déjà Vu	
				N	%
Osborn (19)	1884	—[a]	—[a]	—[a]	50
Lalande (15)	1893	Not specified	—[a]	100	30
Heymans (25)	1906	Psychology students	—[a]	88	63
Chapman and Mensh (26)	1952	Ambulatory clinic patients	Male	110	31
			Female	110	35
McKellar and Simpson (27)	1954	Students	—[a]	110	71
Richardson and Winokur (28)	1967	Neurosurgical patients	Male	93	42
			Female	68	35
		Psychiatric patients	Male	117	40
			Female	184	48
Harper (29)	1969	Health department employees	—[a]	91	63
Brauer et al. (30)	1970	Psychiatric inpatients	—[a]	84	92
Greyson (31)	1977	Schizophrenic patients	—[a]	20	65
		"Nonschizophrenic" patients	—[a]	65	51
Neppe (32)	1979	Members of a cultural society	Female	84	96
Neppe (24)	1983	"Normals"	—[a]	28	68
		"Neuropsychiatric" patients	—[a]	48	73

[a] Information not provided.

have described the déjà vu phenomenon as an experience of a paroxysmal nature lasting from several seconds to several minutes. By calling the experience "subjectively inappropriate," Neppe emphasized that the sense of familiarity is a personal construct that cannot be judged by the outsider. The experience is not so much characterized by the "as if" feeling, as in cases of depersonalization but, rather, by the cognitive dissonance between the feeling that one recognizes a situation and/or sensation and the simultaneous awareness of its impossibility. All of the individual's attempts to provide a definitive explanation for the déjà vu experience prove to be in vain. This often makes for secondary anxiety, a disconcerting tension, or feelings of perplexity. Occasionally, however, the accompanying affect may be pleasurable (37, 38).

By the term "impression" in his definition, Neppe (23, 24) meant to convey that the experience is not solely confined to affect (feelings), thought process (ideas), perception (illusions, recognition), or cognition (remembrance) but entails an amalgamate of perceptive, cognitive, and affective components. In some cases, perception may actually be distorted, even if it is often unnoticed and usually lasts for only a fraction of a second. The stimulus threshold would generally seem to be lowered. For example, for a moment individuals may perceive their environment as looking very much like one of Dali's surrealistic paintings.

The term "familiarity" brings to mind associations with the concept of family. Thus, the term includes both recognition and acquaintance. The recognition pertains to the total situation and/or sensation. Every detail of the present experience is viewed as being identical to an alleged experience in the past, a photographic copy as it were. Sometimes the recognition can be accompanied by the feeling of being able to predict what is going to happen in the next few moments (precognition). To some extent this prediction may also serve as an effort to test the reality content of the déjà vu experience. Neppe used the term "experience" to prevent the limitation of the definition to one modality of perception. By the term "undefined past," he referred to the inability to determine the exact time and place the original experience supposedly took place. Several authors, including Freud (1) and Grasset (39), viewed this inability as an essential component of the déjà vu experience.

These observations pertain in particular to the minor form of the déjà vu experience. This is the form which has been most extensively described in the literature. The major form is generally of prolonged duration. The present experience is perceived as being identical, but not necessarily in every detail. In cases like this, patients may have the impression of having experienced a certain situation and/or sensation on one or even more occasions in the past. The major form of the déjà vu experience is often viewed as an unwanted intrusion. The impression does not disappear after some deliberation, and reality testing remains impaired for a prolonged period of time. The moment that has allegedly been remembered is often localized in time and place and is often incorporated into a delusional system (34).

ETIOLOGY

The déjà vu experience has been associated with many psychopathological disorders—anxiety and dissociative neuroses, mood and personality disorders, schizophrenia, and organic brain syndromes and disorders. In nonpathological conditions, the déjà vu experience can be the result of an emotional trauma, exhaustion, or the use of psychomimetic drugs. The predisposing factors include fatigue, severe stress, and illness (28, 33, 40–45).

The diversity of etiological factors indicates that there is neither a specific nor a pathognomonic relation between the déjà vu experience and any single psychiatric or neurological disorder. Richardson and Winokur (33) suggested that the déjà vu experience may be of help in diagnosing personality disorders. Accordingly, Halgren et al. (46) suggested that the personality structure of patients with temporal lobe epilepsy probably predisposed them to experience déjà vu as an aura. Harper (29), however, found that the déjà vu experience occurred less frequently among individuals with marked neurotic traits.

Richardson and Winokur (33) concluded that the déjà vu experience occurred significantly more often among psychiatric patients than among patients with no psychiatric disorders and patients with cerebral disorders. Lewis et al. (44) found that six female patients with bipolar mood disorders appeared to have psychomotor epileptic symptoms and déjà vu experiences. They concluded that psychomotor symptoms may be more prevalent in bipolar patients than has been recognized.

Of the neurological disorders, the one most widely described as a cause of the déjà vu experience has been temporal lobe or psychomotor epilepsy (22, 47–55). In 1859, Neumann (8) described a déjà vu experience in a female patient with epilepsy. In 1888, Hughlings Jackson (5) suggested that there was a significant relation between the déjà vu experience and disorders of the temporal sphenoidal region of the right hemisphere. In the 1950s this suggestion was confirmed by the experiments of Mullan and Penfield (48): déjà vu experiences were evoked under local anesthesia by electric stimulation of the temporal lobe of patients with psychomotor epilepsy. In a similar study, however, Halgren et al. (46) also found it possible to arouse déjà vu experiences in the nondiseased hemisphere without evoking potentials in the region of the contralateral focus. In 1963, Cole and Zangwill (55) found a significant relation between the déjà vu experience and a focus in the nondominant hemisphere. Although they studied a small number of patients, they concluded that the déjà vu experience should not be viewed as a sign of lateralization. A number of authors (5, 29, 51), in fact, have stressed that a déjà vu experience can be interpreted as an indication of epilepsy only when it occurs in combination with other psychiatric or neurological symptoms.

PSYCHOPATHOGENESIS

Many authors (11, 12, 20, 45, 56, 57) have viewed the déjà vu experience primarily as a disturbance of memory. Similarly, psychoanalytically oriented authors (1, 37, 40, 58–64) have held that a disturbance of memory is involved in the phenomenon and have worked on the assumption that it has some relation to defense mechanisms, dreams, and unconscious fantasies and wishes. According to parapsychologists, the déjà vu experience is based on memories of a past life and thus results from reincarnation (65). Given his term "sentiment of pre-existence," it seems likely that Wigan (4) also associated the phenomenon with reincarnation. Lalande (15) suggested telepathy as a possible explanation. Carrington (66) noted that, in certain cases, the subject may actually have visited the locality in question in his or her astral body while remaining partially conscious.

Various authors (15, 21, 25, 34, 42, 67, 68) have been of the opinion that déjà vu is a disturbance in perception that may be caused by a disturbance of attention rather than a disturbance of memory. Janet (17, 69) held that it entailed an erroneous evaluation of the present perception, which was thought to be the result of a "psycholeptic crisis." The déjà vu experience would thus be viewed as a denial of the present rather than a confirmation of the past.

Numerous authors (25, 29, 40–42, 59, 63, 68–73) have noted the relation between depersonalization and the déjà vu experience. Like Freud (58), Nemiah (74) also held that the déjà vu experience could be viewed as the positive counterpart of depersonalization: "In déjà vu what is, in fact, new, alien, and previously unexperienced is felt as being familiar and as having been perceived before. In contrast, in depersonalization what is actually familiar is sensed as strange, novel, and unreal" (p. 1039). The *jamais vu* experience can be regarded as an extreme degree of depersonalization (73). Neppe (24) suggested that the emphasis in depersonalization is on the experience, whereas the *jamais vu* experience involves situations or places. Nemiah (74) concluded that the déjà vu experience and depersonalization should be regarded as two distinct entities. This conclusion coincides with the findings of Brauer et al. (30). In a group of 84 psychiatric patients, déjà vu experiences correlated with just a few of the variables that depersonalization and derealization correlated with. In a study of the rate of depersonalization in a group of 339 female and 552 male students, however, Myers and Grant (73) reported a significant relation, particularly among the male students, between the déjà vu experience and depersonalization ($p < 0.001$).

Oberndorf (63) and Arlow (40, 75) held that depersonalization and the déjà vu experience were both based on a distortion of the sense of time. Oberndorf (63) was of the opinion that whereas depersonalization is an expression of a major disturbance in reality appreciation, the déjà vu experience is primarily based on a minor distortion in reality perception. Unlike Oberndorf, Arlow (40) felt that there is no perceptual disturbance involved at all and proposed, following Federn (71), that the term "reality perception" be replaced by "sense of reality." Marcovitz (64), however, held that déjà vu experiences, much like hallucinations, certainly do involve a disturbance of perception. The views of Arnaud (14) constituted a synthesis of all the opinions referred to here. According to this French psychiatrist, the phenomenon is based on modifications of the perception mechanism due to disturbance of both memory and attention. In other words, the déjà vu experience can be based on either a perceptual or a mnestic disturbance.

EXPLANATORY THEORIES

As might be expected, the wide range of opinions regarding the basic psychopathogenetic aspects of the déjà vu experience led to an equally wide range of explanatory theories. It would seem that every author who studied the phenomenon with any thoroughness formulated an explanation. The diversity of the hypotheses is obviously due to the fact that a subjective phenomenon like the déjà vu experience does not permit any experimental research. To our knowledge, only three studies provided some experimental evidence. By means of posthypnotic amnesia, Banister and Zangwill (76) succeeded in inducing the feeling of familiarity in three of five subjects. In 1959, Mullan and Penfield (48) reviewed a series of 214 patients treated surgically for relief of temporal lobe seizures. In six of these patients, it was possible to reproduce a déjà vu experience by electrical stimulation of the temporal lobe. More recently, Halgren et al. (46) reported déjà vu experiences evoked by electrical stimulation of the median temporal lobe with stereotaxic-placed depth electrodes in five of 36 subjects with psychomotor epilepsy.

We shall now deal successively with the psychological and neuropsychological hypotheses and the psychodynamic hypotheses and then go on to describe two explanations based on technological models.

Psychological and Neuropsychological Hypotheses

Wigan (4) was of the opinion that the déjà vu experience resulted from the transient nonsimultaneous functioning of the two hemispheres, to each of which he attributed a separate consciousness.

Jensen (9) and Maudsley (77) attributed separate but identical functions to the two hemispheres. The déjà vu experience was thus thought to be based on double perception as a result of an interhemispheric asynchronism, a kind of mental diplopia as it were. Huppert (10) speculated that what was involved was a double image rather than double perception. Dugas (56) held that there was a doubling of the personality. Myers (7) postulated the existence of a subliminal and a supraliminal self ("a part of our mind or faculty which lies below the threshold of our ordinary consciousness"). The déjà vu experience was thus supposedly based on the double perception of the present moment by the subliminal and the supraliminal self.

The explanation provided by Efron (78) was based on advanced neurophysiological research but remained no less speculative. On the grounds of his experiments, Efron hypothesized that information relative to the time of occurrence is transferred from the nondominant to the dominant hemisphere before temporal discrimination of simultaneity and order can take place. The déjà vu experience is supposedly a result of a momentary extra delay in transmission. The dominant hemisphere then receives the same information twice in succession, once directly and once relayed after this delay from the nondominant hemisphere.

Jessen (79) was of the opinion that a déjà vu experience is based on the confusion of a single detail with the whole. The feeling of familiarity that is appropriate to details of earlier experiences is transferred to the present perception as a whole. Neumann (8) presumed that a déjà vu experience emerges if an image based on the present perception is mistaken for a memory. According to Boirac (13), there is more than one possible explanation. A déjà vu experience could be the result of a similarity between a present perception and traces of memories of similar earlier perceptions. A déjà vu experience could also occur if an object aroused the same emotion as some other object seen at some time in the past.

The explanations given by Lalande (15) and Berndt-Larsson (34), which assumed a disturbance of attention, differed only in wording and emphasis. Lalande (15) emphasized a disturbance in perception of time and unconscious perception. Due to reduced attention, seconds seem like minutes and all kinds of images are observed without entering consciousness. After the return to reality, the image that was unconsciously seen several seconds earlier seems like something once seen before in the far distant past. Like Anjel (67), Berndt-Larsson (34) also assumed that conscious perception occurs after sensory data have been intellectually processed.

Due to the reduced ability to maintain attention, a sensory stimulus could be attributed with an intrapsychic representation without intellectual processing. This representation could be mistaken for a memory. MacCurdy (80) was of the opinion that each sensory stimulus immediately and automatically arouses a series of associations with preconscious and unconscious memories. If the present perception is associated with an anxiety-provoking unconscious image, an effort is made to exclude this image from consciousness. The energy of the activated unconscious image is then transferred to the conscious image, which becomes supernaturally real and vivid and amazingly familiar. The active unconscious idea enters consciousness as an affect, i.e., a feeling of familiarity, which is rationalized with the belief that an experience is being relived.

The hypothesis of Siomopoulos (41), formulated in Gestalt psychology terms, exhibits many similarities to the explanation given by Boirac (13), Jessen (79), and MacCurdy (80). Siomopoulos suggested that the déjà vu experience might reflect a disturbance in the organization of perceptual entities and the affective components into larger "object-affect" entities. The feeling of familiarity with the object is thus in fact the awareness of a familiar affect. The similarity between the affects of two object-affect entities was thought to be what led to the recognition of these entities. Parenthetically, this hypothetical process resembles to some extent the process described as redintegration (24).

Krijgers Janzen (38) based his explanation of the déjà vu experience on eidetic imagery. Eidetic imagery is characterized by clear visualization of objects previously seen. The déjà vu experience is thought to be the effect of the interference in perception of objects and eidetic images. The inaccurate projection in time gives the eidetic image the quality of a memory.

Levitan (72) based his explanation on the hypothesis that all perceptions and images are constructed of geometric shapes comprising triangles and rectangles. The déjà vu experience was thus thought to be based on a decomposition of images into these more archaic images, which indeed have been seen before.

Psychodynamic Explanations

In 1907, Freud (1) stated that the déjà vu experience actually pertains to a perceptual judgment resulting from the recollection of an unconscious fantasy or wish. The present perception reactivates the unconscious fantasy or wish that has been formed in the past as a wish to improve the situation. Freud thus felt that the present experience does indeed exhibit a similarity to some experience in the past. However, since this experience has never been conscious, it cannot possibly be consciously remembered. Independently of Freud, Grasset (39) had formulated a similar explanation in 1904. In 1893, Lalande (15) had also presumed that there was some relation between an unconscious observation and the déjà vu experience. The similarity is in fact only superficial and the difference quite essential. Grasset and Lalande alluded to unconsciousness due to an escape from attention as a result of an excess of external stimuli or a reduced perceptual capacity. Freud (1, 58, 59), however, held that it was an internal stimulus, a fantasy or wish, that defense mechanisms prevented from entering consciousness.

Like Freud, most of the later psychoanalytical authors (37, 40, 62, 63) assumed that the déjà vu experience served as a defense mechanism. According to Oberndorf (63), the déjà vu experience represents a kind of reassurance: "There is nothing to worry about, you went through all this once before and came out well. The same will happen this time." Fenichel (81), however, was convinced that the déjà vu experience emerges when the repression has already been completed and the ego is nonetheless reminded of a repressed fantasy or wish against its will. Marcovitz (64) noted that perceptual memory functions would be distorted by the wish for the turning back of time. Like Freud (1), Marcovitz was of the opinion that the déjà vu experience expresses the wish for a second chance; in other words, it was an illusory fulfillment of the wish to repeat a certain experience in such a way that this time the result would accord better with a wish. Marcovitz (64) suggested that the déjà vu experience is better understood if it is thought of as *encore vu*.

Arlow (40) felt that the wish for a second chance was of minor importance and stressed instead the defense function. From a structural point of view, he asserted that the wish came from the ego rather than the id. The present experience simultaneously symbolizes and stimulates the reexperiencing of an anxiety-producing memory, wish, or fantasy. The ego tends to ward off anxiety by various concurrent and complementary defense mechanisms. First, the memory, wish, or fantasy threatening to enter consciousness is neutralized as being unreal, dreamlike, or already past. In order to suppress the significance of the internal sources of anxiety, the original experience is projected or displaced to the present experience. In a psychodynamic sense, the déjà vu experience is thus, according to Arlow (40), comparable to a screen memory as substitute in order to aid the defense mechanism of repression. This view was shared by Boesky (82) and Sohn (83).

Federn (71) explained the déjà vu experience in terms of ego psychology. A déjà vu experience, in his opinion, occurs when a memory in the form of an emerging experience quite transitorily passes the ideational ego feeling boundary, or a perception passes the perceptive ego feeling boundary, first at a moment when the boundary is without narcissistic cathexis, and immediately afterward when it has again received a narcissistic cathexis. The narcissistically blunted boundary takes away the feeling of the present and the evidential feeling, whereas the narcissistically excited boundary imparts them. The speculations of Pacella (84) did not differ essentially from Arlow's conceptions. As a co-worker of Margaret Mahler (85), Pacella (84) explained the déjà vu experience on the basis of object relations theory and the separation-individuation process. The underlying central conflict was shifted from the oedipal phase to the preoedipal period of mental and somatic representations. Pacella felt that the déjà vu experience is an expression of a transient partial regression in the service of the ego to the preoedipal phase as defense against anxiety induced by the present experience.

Many authors felt that there is a possible relation between the déjà vu experience and dreams (15, 60, 61, 70, 86–91). Whereas Lalande (15) held that tracing the déjà vu experience back to a dream is merely a subsequent rationalization, Ferenczi (60, 61) was convinced that the phenomenon was caused by dreams or daydreams, either in the recent or the more distant past. In other words, analogous to the dream as day residue, he viewed the déjà vu experience as dream residue.

In 1909, Freud (86) stated that the déjà vu experience could not only be the result of a dream but could also occur within a dream. A déjà vu experience during a dream about a certain setting or specific place could symbolize the genitals of the mother, a place where one can rightly be said to have actually been before. Pötzl (70) argued that the dream as well as the déjà vu experience could be the result of prematurely interrupted intentions or unfulfilled wishes. Comparing the déjà vu experience to a waking dream, he noted that the situation in which the déjà vu experience occurred might be the realization—as well as the completion with sensory details—of a hitherto unconscious fantasy picture of the particular situation.

Zuger (89) held that the déjà vu experience and the dream were comparable manifestations of one and the same phenomenon. One of the grounds for this conclusion was the occurrence of dreams with contents closely related to the situation of the dreamer at the moment of recalling the dream. In an effort to confirm his view, Zuger studied the possible correlation between dreams and déjà vu experiences in 58 of his psychotherapy patients. In 36 patients, there did indeed prove to be a correlation, and 10 of his patients who reported not dreaming also claimed they had never had a déjà vu experience. On the grounds of nonpsychodynamic considerations, Epstein et al. (90, 91) also assumed the existence of a relation between dreams and déjà vu experiences. These authors suggested that the two phenomena might be the result of uncinate focus discharging.

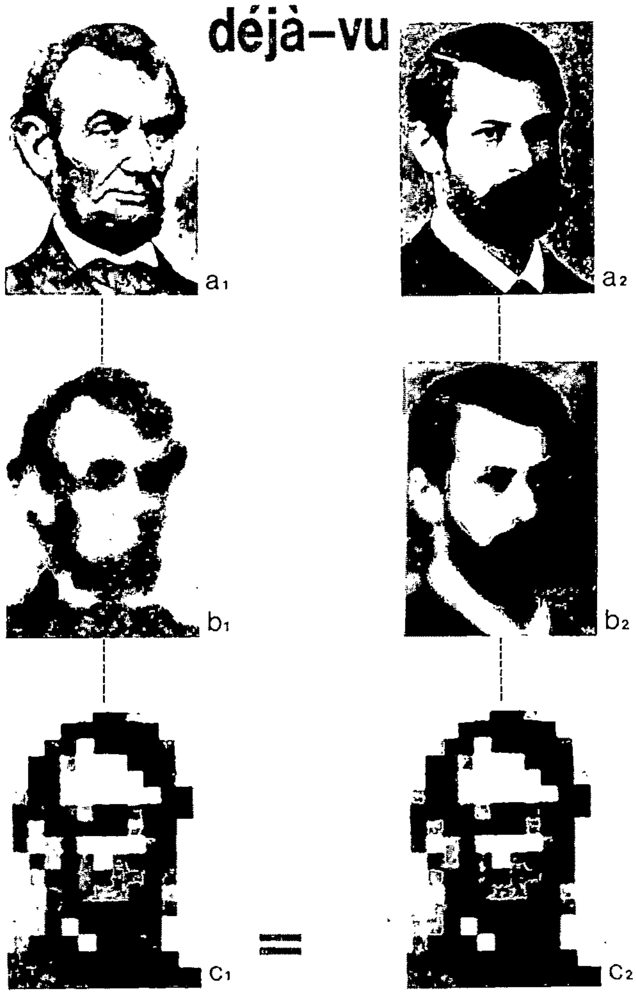
Technological Models

For centuries man has attempted to solve the mystery of memory functioning. Due to the lack of factual evidence, the models used have often been based on the most advanced technology available, such as photography, the audio tape recorder, the computer, and, most recently, holography.

De Nayer (43) suggested that, analogous to the audio tape recorder, the storage of memory items takes place by way of a "recording head" (*tête enregistreuse*) and that the recall of these items occurs by way of a "reproducing head" (*tête lectrice*). The "tape" of the memory consists of a set of "printing cases" (*cases à engrammer*). De Nayer (43) pictured the two heads floating freely in the memory above the fixed set of printing cases. The déjà vu experience occurs if and when, due to a certain disorder in the coordination, the two heads float above the same printing case at the same time, so that the information is simultaneously recorded and reproduced. In other words, the information is perceived and remembered simultaneously, so that the present perception is experienced as a memory.

Up to now, holography has not been used as a memory model to explain the déjà vu experience. Holography is a form of three-dimensional photography. In addition to information about wave length and amplitude, the phase of light waves is also fixed on a film or on a glass plate with a photosensitive emulsion. Thus, every part of the plate contains all the information needed for the reconstruction of the entire picture. So, in principle, even the smallest fragment would give the complete picture, although the smaller the fragment, the less sharp the picture would be. According to this model, memories are stored in the brain as holograms. This model can serve to explain why a complete memory can be reconstructed by stimulating a section of the brain and at the same time why this memory does not disappear after the section of the brain has been removed.

FIGURE 1. Hologram Model for the Déjà Vu Experience



In terms of the hologram model (see figure 1), the déjà vu experience takes place if a section of the hologram of the present perception (c1) that is to be stored in the memory is identical to the mnestic information of a section of a different hologram picture (c2) that was recorded at some moment in the past. Although the two complete pictures (a1 and a2) bear little or no resemblance to each other, as a result of the mismatching of the two virtually identical sections of the holograms (c1 and c2), the individual feels certain he or she has seen the picture (a1) before at some moment in the past.

As a mnestic model, the hologram can be relevant to the relation between the brain function and the subjective déjà vu experience. The explanation based on this model resembles the one given by Levitan (72), which was also based on similarities between components of the present perception and components of the already existing images.

CONCLUSIONS

A subjective and nonspecific phenomenon like the déjà vu experience can easily escape the attention of clinical investigators, who are focused on reliability and validity. This might explain why the symptom has not been included in *DSM-III-R*. In our opinion, however, the déjà vu experience can indeed be of importance in a psychopathological sense. The déjà vu experience would seem to belong to the same category as depersonalization (including the *jamais vu* experience). However, since each of these phenomena sometimes requires a very different psychopathogenetic explanation, they should be viewed as distinct entities. One of the factors that make the déjà vu experience important is the possible adaptive function in reducing unpleasant affects, the function of defense. It can be helpful to discuss this function with a patient in order to understand the psychodynamics of a patient's personality disorder. The déjà vu experience can also be indicative of epilepsy, particularly in combination with other psychiatric and/or neurological symptoms. In addition, its importance is related to the frequency of occurrence. The déjà vu experience is a ubiquitous and often impressive phenomenon. Consequently, almost everyone is familiar with it. Discussing this experience will thus likely inspire confidence, which can be of importance for the working alliance with the patient.

Lastly, the déjà vu experience can serve as an intriguing point from which to approach the study of the processes of memory storage and perception. The explanation based on the hologram model implicitly confirms the view expressed by Arnaud (14) and Janet (17, 69) that the déjà vu experience is not solely the result of a memory disorder but involves an erroneous interpretation (mismatching) in the memory of the present perception, possibly due to a disturbance of attention. In other words, a déjà vu experience should be regarded as a disturbance of apperception. Consequently, the phenomenon may be related to a disturbance of memory, perception, or attention or to an impaired integrative functioning of the ego. All of these disturbances can be due to an impaired functioning of the brain. The reasons for a déjà vu experience, perhaps in the absence of any underlying organic cause, are best clarified by the psychodynamic explanations.

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Predictions About New Long-Stay Patients: Were They Valid?

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During 1979–1989, the long-stay population in Massachusetts state psychiatric hospitals declined and then moderately increased, although to far below its initial 1979 level. The increase toward the end of the period was due to a growing number of patients admitted, an increase in the proportion of these new patients who were retained for 1 year or longer, and a decrease in discharges of long-stay patients, especially those hospitalized for 20 or more years. The last factor was particularly important and was due to the fact that the number of these very-long-stay patients had become so small by 1983 that the effect of their continued discharge on the total long-stay population was minimal. The authors point out that more community services, not more hospital beds, may be needed. They recommend that states assess the clinical needs of the long-stay population before determining how to allocate their resources to address this phenomenon.

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Early in the community mental health movement it was thought that the role of state hospitals in the care of long-term patients would gradually disappear as hospitals' functions were replaced by community services. In the 1970s and early 1980s, however, authors in Europe (1–7) and the United States (8–11) described a population of new long-stay patients and questioned whether these patients would accumulate in public hospitals and ultimately replace the old long-term patients, whose numbers had been declining over the past two decades.

Platman and Booker (9) studied seven cohorts of patients admitted to all Maryland state hospitals each year between 1976 and 1983. They found that a new long-stay population was not accumulating and concluded that there was no basis for the concern that these patients would slow the attrition of long-term patients. Craig et al. (11), in contrast, followed for 1 year a cohort of patients admitted in 1975 and 1976 to one state hospital in New York State and concluded that the population of new long-stay patients was growing and would probably continue to do so in the future. Craig et al. further implied that other places in the nation would probably experience similar phenomena, since in their study the accumulation occurred despite the existence of a richly endowed community mental health system. Among the limitations of their study was the inclusion of only one state hospital, raising the question of whether this hospital was representative of the rest of the New York State public hospitals. Moreover, the patient cohort was followed for only 1 year after admission, which severely limited the scope of the study and the basis for the authors' predictions. Kastrup (12) successfully avoided these limitations in a nationwide study of Danish inpatients admitted to psychiatric hospitals over a 10-year period beginning in 1970. Although he too found an accumulation of long-stay patients, he suggested that this may have been partially due to the lack of alternative community settings, not simply the psychopathology of the patients.

Taube et al. (13) studied the lengths of stay of patients who resided in a national sample of state hospitals in 1979 and found a relatively large group of new long-stay patients in 1979, but he stated that predicting whether this population would grow or not was risky, since it depended on so many factors that could not be determined without longitudinal data. One of

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TABLE 1. Yearly Census and Discharge of Patients in Massachusetts State Psychiatric Hospitals During 1979–1989, by Length of Stay

	Census at Beginning of Year, by Length of Stay							Discharges and Deaths During Year, by Length of Stay					
	Number				Percent of Total			Number			Percent of Census for Length-of-Stay Group		
Fiscal Year	<1 Year	1–5 Years	>5 Years	Total	<1 Year	1–5 Years	>5 Years	<1 Year	1–5 Years	>5 Years	<1 Year	1–5 Years	>5 Years
1979	1,167	747	998	2,912	40.1	25.7	34.3	884	248	241	75.7	33.2	24.1
1980	1,113	714	825	2,652	42.0	26.9	31.1	888	268	194	79.8	37.5	23.5
1981	986	611	691	2,288	43.1	26.7	30.2	794	231	196	80.5	37.8	28.4
1982	1,026	486	581	2,093	49.0	23.2	27.8	790	180	143	77.0	37.0	24.6
1983	986	484	496	1,966	50.2	24.6	25.2	714	126	115	72.4	26.0	23.2
1984	1,051	585	426	2,062	51.0	28.4	20.7	822	162	96	78.2	27.7	22.5
1985	1,100	608	374	2,082	52.8	29.2	18.0	838	180	73	76.2	29.6	19.5
1986	1,109	636	355	2,100	52.8	30.3	16.9	869	233	81	73.4	36.6	22.8
1987	1,348	557	360	2,265	59.5	24.6	15.9	951	136	54	70.5	24.4	15.0
1988	1,034	743	381	2,158	47.9	34.4	17.7	757	194	35	73.2	26.1	9.2
1989	974	767	405	2,146	45.4	35.7	18.9	—	—	—	—	—	—

these factors was found by Hogg and Brooks (14) to be a degree of arbitrariness in staff planning for disposition. For example, Hogg and Brooks could not find any clinical, demographic, or social variables that distinguished new long-stay schizophrenic patients in three Scottish inpatient facilities from new long-stay schizophrenic patients in day hospitals. McCreadie et al. (15), in a cross-sectional study of new long-stay patients in Scotland in 1982, demonstrated a wide variation in the accumulation of new long-stay patients among hospitals and suggested on the basis of their data that staff attitudes toward discharge may have been partially responsible for this variation.

Several problems prevent precise comparisons among the previous studies. First, the definition of short- and long-stay patients varies among reports. A short-stay patient in one study is defined as a long-stay patient in another. Second, the index years used in the studies to distinguish between new and old long-stay patients are not identical. Third, the period over which a given admission cohort is followed, which forms the basis for the authors' conclusions, differs from study to study and in at least one case is as short as 1 year.

Most of the foregoing studies were conducted before 1982. On the basis of their findings, conflicting predictions were made about the extent to which new long-stay patients would accumulate in public hospitals in the future and replace the declining numbers of old long-stay patients. To our knowledge, since the publication of these early studies there has not been a systematic examination of the validity of these predictions. This is surprising because the net balance of long-stay patients profoundly affects assessment of the success of deinstitutionalization with even the most narrow criteria. Moreover, this phenomenon has important policy and planning implications for the roles, functions, organization, staffing, and funding of both state hospitals and community programs in the future. In this report we examine the earlier predictions about the net accumulation of long-stay patients by investigating this phenomenon in the public hospitals of Massachusetts.

METHOD

We examined the lengths of stay of patients residing in all eight Massachusetts state psychiatric hospitals during the 10-year period from the beginning of fiscal year 1979 to the beginning of fiscal year 1989; our data were obtained from the Massachusetts Department of Mental Health. Lengths of stay were grouped into three categories: short (up to 1 year), moderately long (between 1 and 5 years), and very long (more than 5 years). Thus, for the purpose of this study patients were defined as long-stay if their hospital tenure was at least 1 year and as short-stay if their hospital tenure was under 1 year. Patients were defined as new if they were admitted after the end of fiscal year 1978 and as old if they were admitted on or before this date. A new long-stay patient was therefore anyone admitted after the end of fiscal year 1978 who remained for at least 1 year. An old long-stay patient was anyone who had been admitted before the end of fiscal year 1978 and remained for at least 1 year. We examined data on annual admissions and discharges (which were defined consistently for this period and did not include visit status but, for the purposes of this paper, did include deaths) broken down by length of stay. For certain analyses, the data were aggregated into two periods: the beginning of 1979 through the beginning of 1984 and the beginning of 1984 through the beginning of 1989.

RESULTS

Changes in Census of Length-of-Stay Groups

Between 1979 and 1989, the total state hospital census decreased from 2,912 to 2,146. When the contin-

TABLE 2. Yearly Census and Percent Change During 1979–1989 for Patients Hospitalized in Massachusetts State Hospitals for More Than 5 Years

	Census at Beginning of Year, by Length of Stay							
	5–10 Years		10–20 Years		Over 20 Years		Over 5 years	
Fiscal Year	Total	Change	Total	Change	Total	Change	Total	Change
1979	267	—	266	—	465	—	998	—
1980	238	−29	215	−51	372	−93	825	−173
1981	215	−23	173	−42	303	−69	691	−134
1982	218	+3	143	−30	220	−83	581	−110
1983	212	−6	115	−28	169	−51	496	−85
1984	185	−27	103	−12	138	−31	426	−70
1985	178	−7	94	−9	102	−36	374	−52
1986	188	+10	85	−9	82	−20	355	−19
1987	195	+7	97	+12	68	−14	360	+5
1988	222	+27	100	+3	59	−9	381	+21
1989	239	+17	108	+8	58	−1	405	+24

TABLE 3. Change in Census of Massachusetts State Psychiatric Hospitals During 1979–1984 and 1984–1989, by Length of Stay

	Stay=<1 Year		Stay=1–5 Years		Stay=>5 Years		Total	
Fiscal Year	N	%	N	%	N	%	N	%
Census at beginning of year								
1979	1,167	40.1	747	25.7	998	34.3	2,912	100.0
1984	1,051	51.0	585	28.4	426	20.7	2,062	100.0
1989	974	45.4	767	35.7	405	18.9	2,146	100.0
Change								
1979–1984	−116	−9.9	−162	−21.7	−572	−57.3	−850	−29.2
1984–1989	−77	−7.3	+182	+31.1	−21	−4.9	+84	+4.1

uous data were examined (table 1), it became clear that the decrease in census occurred entirely within the first 5-year period. After this, the census gradually, although inconsistently, increased. This increase was due primarily to changes within the long-stay hospital population.

Specifically, the increase in total hospital census between 1984 and 1989 was due to a reversal of the initial decline in the number of patients with moderately long stays in combination with the leveling off of what had been a sharp decline in the number of patients with very long stays. Detailed examination of this latter category (table 2) revealed the importance of the subgroup of patients who had resided in the hospitals for more than 20 years. The decline in this subgroup during 1979–1984 had the greatest impact on the total hospital census. If this subgroup had continued to decline to the same degree during 1984–1989, even the increase in the number of patients with moderately long stays would not have been sufficient to change the direction of the total census.

Table 3 summarizes the changes that took place in the census of the state psychiatric hospitals within the two periods, 1979–1984 and 1984–1989. The number of short-stay patients declined minimally during both periods, the number of patients with moderately long stays decreased substantially and then rose to beyond its original level, and the number of patients with very long stays showed the greatest decrease of any category, almost all of which occurred in the first 5-year period, after which the number remained relatively stable. The total long-stay population in consequence decreased markedly in the first period (by 42%, from 1,745 to 1,011) and then grew moderately during the second (by 16%, to 1,172), though to far below its initial 1979 level.

What factors led to the reversal of the census trend in the moderately-long-stay category between the two periods? Table 4 demonstrates that this reversal resulted from the combination of an increase of 197 (from 1,208 to 1,405) in the number of entrants into this length-of-stay category and a decrease of 148 (from 1,053 to 905) in the number of discharges from it between the two periods. In contrast, the numbers of patients who moved from this category into the very-long-stay category during the two periods were virtually the same.

The increase in the number of entrants into the moderately-long-stay category between the first and second periods was due to an increase of 2,145 in the total number of admissions to the hospitals (which grew in aggregate from 30,867 to 33,012) and an increase in the percentage of admitted patients whose hospitalizations continued into the second year (from 3.9% to 4.3%) (table 4). Although these two factors contributed almost equally to the growth in the number of entrants into the moderately-long-stay category, there was a major difference in their time courses. Whereas

TABLE 4. Changes in Census During 1979–1989 for Patients Hospitalized in Massachusetts State Psychiatric Hospitals for 1–5 Years

		Patients Hospitalized 1–5 Years							
						Removed From 1–5-Year Group			
		Beginning of Year		Entered 1–5-Year Group		Were Discharged or Died		Entered >5-Year Group	
Fiscal Year	Total Admissions in Prior Year	N	Change From Prior Year	N	% of Prior Year Admissions	N	% of Census at Beginning of Year	N	% of Admissions in Year of Admission
1979–1983									
1979	5,980	747	—	283	4.1	248	33.2	68	1.1
1980	6,758	714	−33	225	3.3	268	37.5	60	0.9
1981	5,610	611	−103	192	3.4	231	37.8	86	1.2
1982	5,512	486	−125	236	4.3	180	37.0	58	0.9
1983	6,007	484	−2	272	4.5	126	26.0	45	0.6
Total	30,867	—	—	1,208	3.9	1,053	34.6	317	0.9
1984–1988									
1984	6,398	585	+101	229	3.6	162	27.7	44	0.7
1985	6,771	608	+23	262	3.9	180	29.6	54	1.0
1986	6,360	636	+28	240	3.8	233	36.6	86	1.6
1987	6,929	557	−79	397	5.7	136	24.4	75	1.3
1988	6,554	743	+186	277	4.2	194	26.1	59	0.9
Total	33,012	—	—	1,405	4.3	905	28.9	318	1.1
1989	—	767	+24	—	—	—	—	—	—

TABLE 5. Change in Census During 1979–1984 and 1984–1989 for Patients Hospitalized in Massachusetts State Psychiatric Hospitals for 1 or More Years, by Date of Admission

	Patients Hospitalized 1 or More Years					
	Admitted Before End of 1978		Admitted After End of 1978		Total	
Fiscal Year	N	%	N	%	N	%
Census at beginning of year						
1979	1,745	100.0	0	0.0	1,745	100.0
1984	426	42.1	585	57.9	1,011	100.0
1989	166	14.2	1,006	85.8	1,172	100.0
Change						
1979–1984	−1,319	−75.6	+585	—	−734	−42.1
1984–1989	−260	−61.0	+421	+72.0	+161	+15.9

the increase in hospital admissions occurred fairly consistently during the second period, the major increase in the retention rate occurred during only one year, 1987. Curiously, the increased number of admissions did not result in an accumulation of short-stay patients.

The New Long-Stay Patient

Another perspective on changes in length of stay among the state hospital population is gained by dividing the long-stay patients into new and old on the basis of their dates of admission and comparing changes in the populations of the resulting two subgroups (table 5). Such a comparison demonstrates that in the first period the decrease in the old long-stay patients so far exceeded the increase in new long-stay patients that the total long-stay population dropped markedly. In the second period, the decline in the old long-stay patients slowed dramatically owing to the small number of these patients who remained in the hospital at the beginning of this period. In contrast, new long-stay patients continued to accumulate. The result was a net increase in the number of long-stay patients during the second period, leading to an overall second period growth in the total long-stay population and in the total hospital census, although far below their 1979 levels. As these figures indicate, the sharp slowing in the decline in the number of old long-stay patients was even more important in the dynamics of the hospital census than the increase in new long-stay patients. The result was that some long-term beds that had been closed as the old population had left the hospital during the first period had to be reopened to accommodate the new population in the second. We are presently attempting to analyze the demographic and clinical characteristics of old and new long-stay patients to determine whether these two subgroups of patients differ from one another and in what respects.

DISCUSSION

In the early part of the 1980s, contradictory predictions were made regarding the accumulation of long-stay patients and the effect this would have on the overall state hospital census. It is clear that in Massachusetts the total number of patients with moderately and very long stays declined markedly between 1979 and 1989. This drop in turn decreased the total hospital census during this time. Ten-year summary data mask the fact that after reaching a nadir in 1987 the number of long-stay patients began to increase again. This appears to be a combined result of the decline in the number of old long-stay patients discharged and the continued growth in the number of new long-stay patients.

Some authors have postulated that the state hospital will gradually assume a greater role in providing indefinite asylum for patients with very long stays (>5 years), who are probably not going to improve with the currently available therapies and have nowhere else to go. Our data do not support this prediction. When one examines the census of the patients with very long stays as a proportion of the total Massachusetts state hospital census, it becomes clear that the role of the state hospital in the care of these patients shrank rapidly during the first period and has remained relatively small since then, in both absolute and relative terms. The number of such patients (and their percentage of the total hospital census) was 998 (34%) in 1979, 426 (21%) in 1984, and 405 (19%) in 1989. Whether this trend will continue will in part depend on whether the new long-stay patients (who have been responsible for the recent increase in the moderately-long-stay category) remain hospitalized long enough to become very-long-stay patients in larger numbers than are offset by placement of these patients into alternative long-term facilities, such as nursing homes and community residential settings. Table 2 suggests that this accumulation is beginning to occur already. What we can be certain of is that unless there is some change in the factors that led to the net accumulation of new long-stay patients in the past 5 years, the hospital census is likely to increase. This is because the offsetting effect of the decline in the number of old long-stay patients will inevitably continue to diminish. Even if a large percentage of old long-stay patients leave the hospitals in the future, their absolute number is now so low that their influence on the total census would be minimal.

It has been predicted that despite the growth of community hospital psychiatric units, the state hospital will continue to provide acute care for very disturbed patients. Our data support this prediction. The percentage of patients in the short-stay category increased between 1979 and 1989 from 40% to 45% of the total hospital population, although in absolute terms the number of such patients decreased by 193.

To understand why on balance the long-stay population began growing since 1987 we have to examine the factors that have increased the hospital admission rate and decreased the number of discharges of long-stay patients. There may be an increase in the complexity and degree of disturbance of patients seeking admission, a relaxation in the criteria for admission, and/or a greater hesitancy of hospital staff to discharge patients who have previously proven unsuccessful at living in the community. These factors in turn may have been influenced and compounded by the decrease of federal support for low-cost housing, community mental health, and social services in the past 8 years and by the "gentrification" of the urban housing in many cities. There may also have been a saturation of existing residential settings for the mentally ill in the community. Every assessment of the state hospital population undertaken in Massachusetts in the last decade has demonstrated that despite the existence of over 3,000 beds in staffed community residences, the continued insufficiency of such beds remains the biggest major barrier to the discharge of long-stay patients. At the last count, in May 1989, 359 state hospital patients were awaiting placement in then still unavailable community residential settings (Hospital Scorecard, Massachusetts Department of Mental Health, 1989).

Finally, the large pool of very-long-stay patients that existed in the past and whose discharge was the major cause of the census decline between 1979 and 1984 was depleted by the mid-1980s and thus was diminished as a source of further census decreases. The patients with very long stays were by and large older and may have had more manageable symptoms than the moderately-long-stay patients; they were thus initially more easily placed in nursing homes and other residential settings. By the second period, the older patients who were left behind in the hospitals may have been more difficult to place because their symptoms were more severe and fewer nursing home beds were available. The decreased availability of nursing home beds was due to the growing competition for such beds as the general population ages and to changes in federal legislation that have restricted the admission of mentally ill patients to nursing homes.

Implications for Public Policy

What are the public policy implications of this very recent, although modest, increase in long-stay patients in state mental hospitals if this trend continues? It is tempting to conclude that states should build additional hospitals or refurbish existing ones to deal with this increase. Certain states have in fact done this in a reflex manner without regard for the clinical needs of the population, arguing that if the census is growing, more state hospital beds are needed. However, our data do not necessarily point to this conclusion. It would be equally reasonable for states to further develop community residences and other community services. In fact, if the Massachusetts data on state hospital patients awaiting placement are representative, a larger investment in community residential settings seems more sensible. The choice is between accommodating the higher hospital census or altering it, and the states' decisions will have a crucial and long-term impact on the fate of thousands of chronically mentally ill patients. If scarce public resources are used to increase the number of hospital beds for long-term patients without regard to the needs of many of these patients for other kinds of clinical services and settings, the resources necessary to develop the latter will not be available. In this period of limited resources, one option is likely to foreclose the other.

It is important as a next step to determine whether our findings are representative of the experience in other parts of the country. If so, we must carefully assess the biopsychosocial needs of this growing long-stay population so that psychiatrists and policy makers can respond on the basis of clinical need rather than dogma or political expediency.

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An Empirical Literature Review of Definitions of Severe and Persistent Mental Illness

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Seventeen definitions of the severely and persistently mentally ill have appeared in the literature over the past decade. These definitions have been used by 13 authors to formulate service programs and to estimate the prevalence of serious mental illness in the population. To test the applicability of these definitions, the authors operationalized each definition and applied it to a representative sample of 222 patients receiving services in one of Philadelphia's inner-city neighborhoods. The analysis showed estimates of prevalence of serious mental illness ranging from 4% to 88% of the treated population, depending on the definition applied. The NIMH (1987) definition was representative of the middle-range estimates of 45% to 55% arrived at by eight authors.

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There is a rich history of definitions of the severely and persistently mentally ill that spans the past two decades. Early definitions were based primarily on prior or current care in state institutions, since most seriously ill patients were residents of state mental hospitals. The advent of deinstitutionalization and the emergence of a treatment philosophy entailing service provision in the community created a need to redefine this population. The late 1970s began a period of proliferation of definitions of the seriously mentally ill among clinicians, policy makers, and researchers (1, 2). Focus shifted away from inpatient care as the critical element for defining the seriously mentally ill to criteria such as psychiatric diagnosis, functional disability, and illness duration (3). Conceptually, the definition of seriously mentally ill individuals as "persons who have severe and persistent disabilities that result primarily from mental illness" is well accepted (4). However, it is in specifying the relevant diagnostic categories, the nature and degree of disability, the length of illness, and the relative importance of each that differences arise.

In 1987, a workgroup sponsored by the National Institute of Mental Health (NIMH), which convened to formulate a consensus definition of the severe and persistent mentally ill (1), suggested that a "tower of Babel" still exists among persons who speak of serious mental illness. Selecting criteria that can be used to identify persons with severe and persistent mental illness in the population is difficult given the episodic nature of mental illness, fluctuations in the severity and duration of mental disability over time, and the variability in service utilization patterns across providers and states. National mental health policy initiatives such as the NIMH Community Support Program (5) and the Robert Wood Johnson Foundation program on chronic mental illness (6) contributed to a proliferation of definitions of the seriously mentally ill as each community program sought to meet its own needs. These initiatives also provided an impetus to standardize definitions for the purpose of program evaluation.

This paper reports on a review of 17 definitions of the severe and persistent mentally ill that have appeared in the literature over the past decade. Each of the definitions was operationalized and applied to a representative sample of patients receiving services in one of Philadelphia's inner-city neighborhoods. Depending on the specific definition applied, we found great variance in prevalence estimates of serious mental illness in this treated population residing in the community. These findings have implications for policy makers and service system planners who are involved in targeting resources to enhance the appropriateness and quality of care provided to this population.

METHOD

From the large number of definitions of the seriously mentally ill in the literature, 17 (representing 13 authors) were selected for inclusion in this study. This selection was based on the following criteria: the definition pertained to the period after deinstitutionalization, it was developed in the context of mental health care in the United States, and it was specific enough to be readily operationalized.

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Whereas two documents represent government definitions (5, 7), most articles present the views of authors who are academic researchers. The articles containing the definitions were written for different reasons. Six estimated the prevalence of chronic mental illness in the population (8–13), while the remaining five focused on service policy (14–18). Numerous other authors reference the NIMH 1977 definition (5) (NIMH 1) in their studies (19–24). Their definitions are subsumed under the NIMH 1977 definition (5), although minor departures may have been suggested by these authors.

The columns of table 1 contain a complete listing of the definitions operationalized in this study. Two authors had multiple definitions. The rows of the table contain a listing of the detailed criteria used by each author, organized into three major categories: diagnosis, disability, and duration. Thus, for example, the NIMH 1987 definition (7) (NIMH 2) requires that an individual meet criteria in all three categories in order to be considered as having a serious mental illness.

Minkoff's characterization of chronic mental illness (15), although more than a decade old, clearly describes the conceptual underpinnings of the contemporary definition of serious mental illness. He describes three distinct groups: the chronically mentally ill, the chronically mentally disabled, and the chronic mental patient. The chronically mentally ill are defined by diagnosis even though the symptoms of illness are not always present. The chronically mentally disabled are characterized by "partial or total impairment of instrumental role performance (usually vocational or homemaking). In addition to performance, the extent of disability is related to the degree of social inadequacy, symptomatic impairment and the need for external support or treatment." The chronic mental patients are a subgroup characterized by institutionalization, with "chronicity in this group associated with the duration and continuity of hospitalization and sometimes with the number of hospitalizations." The current view of the seriously mentally ill most closely resembles Minkoff's description of the chronically mentally disabled.

There is general agreement among the 13 authors that diagnosis, disability, and duration criteria in some form are necessary to define serious mental illness. The differences relate to the exact specification and relative importance of each criterion. There is considerable agreement about the categories that should be included within disability and diagnosis. However, it is evident from the diverse criteria used to define duration or service utilization that the criterion chosen by each author often depended on the data the particular author had access to rather than on the services that the author considered relevant.

Diagnosis forms the basis for defining the population at risk. In nine of the 17 definitions the authors chose to delineate those disorders which may be associated with serious mental illness, thereby excluding the others. In all nine cases the authors agree on nonorganic psychoses such as schizophrenia and major affective disorders. Five of the nine authors suggested that organic psychosis, alcohol and drug dependence, and mental retardation should also be included. One author included neuroses and other nonorganic disorders in addition to nonorganic psychoses. In the remaining eight definitions, no explicit reference to diagnosis by the author was interpreted to mean that any mental disorder may result in serious illness.

Disability was identified as a criterion of serious mental illness in 13 of the 17 definitions. Most authors agree on the set of relevant categories of dysfunction that should be considered and that more than one should be present. There is, however, considerable ambiguity about the appropriate combination of the various categories and their relative importance.

Due to the differences among authors regarding the proper measure of time or frequency of service utilization constituting chronicity, duration of illness is the most problematic of the three criteria. It was indicated as a necessary condition of chronicity in 15 of the 17 definitions. While several authors looked at the overall length of time that the illness and/or treatment persisted, others made the duration criterion contingent upon some minimal length of stay in a hospital, institution, or residential or partial care setting or on some frequency of service utilization within a designated time period.

Using the narrative descriptions of severe and persistent mental illness, we operationalized each criterion and coded it in a computer program containing the variables describing patient attributes and history of illness and care. In order to ensure an accurate interpretation, the definitions were operationalized independently by each of the authors of this paper. Differences in interpretation were discussed, and in a number of cases the authors of the definitions were contacted for clarification. The NIMH 1987 definition (7) will be used to illustrate how the definitions were operationalized.

In the NIMH 1987 definition (7), diagnosis was described as a nonorganic psychosis or personality disorder (*ICD-9*, pp. 299 and 301). Disabilities that met the conditions of the definition were found in at least three of the following five categories of dysfunction: social behavior demanding intervention by mental health system or courts, mild impairment in activities of daily living and basic needs, moderate impairment in social functioning, moderate impairment in performance at work, and moderate impairment in nonwork activities. The duration criteria described the seriously mentally ill as having a history of previous hospitalizations or outpatient treatment accompanying an illness and disability over a long period of time. In addition, persons in the population of concern generally require long-term treatment, rehabilitation, or support services. In operationalizing this criterion, we used variables that identified people who had a 2-year history of mental illness or were in treatment for 2 years or more. A complete description of the operationalization

TABLE 1. Definitions of Severe and Persistent Mental Illness[a]

Criteria	NIMH 1 1977 (5, 19–24)	NIMH 2 1987 (7)	Krute et al. (12)	Minkoff (15)			Test et al. (16)
				1	2	3	
Diagnosis (*ICD-9*)							
Nonorganic psychoses and personality disorders	XXXX	XXXX	OR	OR	OR	OR	OR
Organic psychoses			OR	OR	OR	OR	OR
Alcohol and drug dependence			OR	OR	OR	OR	OR
Mental retardation			OR	OR	OR	OR	OR
Neurosis and other nonorganic categories			OR				OR
Disability							
SSI/SSDI							
Social behavior demanding intervention by mental health system or courts		OR3					
Limited ability to obtain needed assistance	OR0	OR0					
Impaired activities of daily living and basic needs	OR3	OR3	OR2				OR3
Impaired social functioning	OR3	OR3			OR3	OR3	OR3
Limited and impaired performance in employment	OR3	OR3	OR2		OR3	OR3	OR3
Limited and impaired performance in nonwork (e.g., leisure, homemaking)	OR3	OR3	OR2		OR3	OR3	OR3
Reliance on psychosocial, drug, or other supports					OR3	OR3	OR3
Vulnerability to stress		OR0					OR0
Disability that prevents self-sufficiency and causes dependency		OR0	OR0				OR0
Duration							
Prolonged illness and long-term treatment		XXXX					XXXX
Illness of at least 3 months			XXXX				
Illness or treatment of at least 12 months							
Hospitalization							
3 months or less							
3–12 months (in 1 year)							
6 months or more (1 episode in past 5 years)	OR						
12 months or more (in past 5 years)							
Institutionalization (current or prior)						XXXX	
2 or more hospitalizations (within 1 year)	OR						
Residential/nursing/home placement							
2 or more admissions							
Partial care							
2 or more admissions							
Outpatient							
No treatment at present (despite prior hospitalization)							

[a] XXXX=required criterion; OR=requires only one of the designated criteria; XXX=requires only schizophrenia; OR3=requires only three of the designated criteria; OR2=requires only two of the designated criteria; OR0=criterion given in definition, could not be operationalized.

of all the author definitions is found in a Wharton Policy Modeling Workshop working paper (25).

Study Population

A stratified sample of 222 adult patients who were admitted to an inner-city community mental health center (CMHC) in the city of Philadelphia between January 1981 and December 1984 and used mental health services between July 1984 and June 1986 was selected for this analysis. This sample is representative of an inner-city catchment area population that consisted of a large number of Medicaid recipients (60%) and a high percent of Medicaid clients who are recipients of Supplemental Security Income benefits (41%). The 222 study subjects in this catchment area were

TABLE 1. (continued)

Turner et al. (17)	Peele et al. (18)	Strauss (14)	Goldman et al. (9)	Szymanski et al. (13)			Ashbaugh et al. (10)	Ashbaugh et al. (11)	Hargreaves et al. (8)
				1	2	3			
OR	OR	OR	OR	OR	OR	XXX	OR	OR	OR
OR	OR		OR	OR	OR		OR	OR	
OR	OR		OR	OR	OR		OR	OR	
OR	OR		OR	OR	OR		OR	OR	
OR	OR	OR		OR	OR		OR	OR	
			OR					OR	
	OR2								OR2
OR0	OR2								
OR			OR3						OR2
OR		XXXX	OR3						OR2
		XXXX	OR3				OR		OR2
			OR3				OR		OR2
	OR2								
OR0									
	OR0		OR0						OR0
XXXX	XXXX	XXXX	XXXX						
						XXXX	XXXX		
				XXXX				OR2	OR
			OR						
			OR						
			OR						
			OR						OR
					XXXX			OR	
			OR	OR				OR2	OR
								OR0	
			OR	OR				OR2	OR
								OR	
			OR	OR					
			OR						

predominantly black (89%, N=198), unmarried (60%, N=133), and between the ages of 21 and 39 (62%, N=138); 36% (N=80) had a diagnosis of schizophrenia or affective disorder. This high-risk population was selected because it was likely to have a large percentage of individuals who exhibited characteristics associated with severe mental illness.

A comprehensive psychiatric service history was constructed for each of the patients by integrating seven databases containing information from the state hospital, general hospitals, county forensic unit, catchment area emergency room, and all outpatient and partial care contacts with community providers over a 2-year period. The integration of service data was necessary because of the fragmented nature of the service system in the community and the limited number of variables found in each database. In addition, clinical information from the catchment area CMHC was abstracted from patient records. These records contained detailed information on duration of illness, disability, employment history, diagnosis, symptoms, mental health status, and a variety of demographic and social variables (26). The definitions of severe and persistent mental illness cited in table 1 were applied to this sample, and prevalence estimates were developed for each of the 17 definitions.

RESULTS

Prevalence estimates of severe and persistent mental illness in the Philadelphia inner-city treated population are given in figure 1. Two estimates are provided for each definition and are based on two different duration criteria. The first is determined by either the patient's assessment of whether the illness exceeded 2 years or by a documented service history of 2 years or more. The second is based solely on the service history variable. We regard the first criterion as more appropriate but offer the latter as a sensitivity analysis to highlight the effect of different measures of duration on estimates of prevalence of serious mental illness in a treated population.

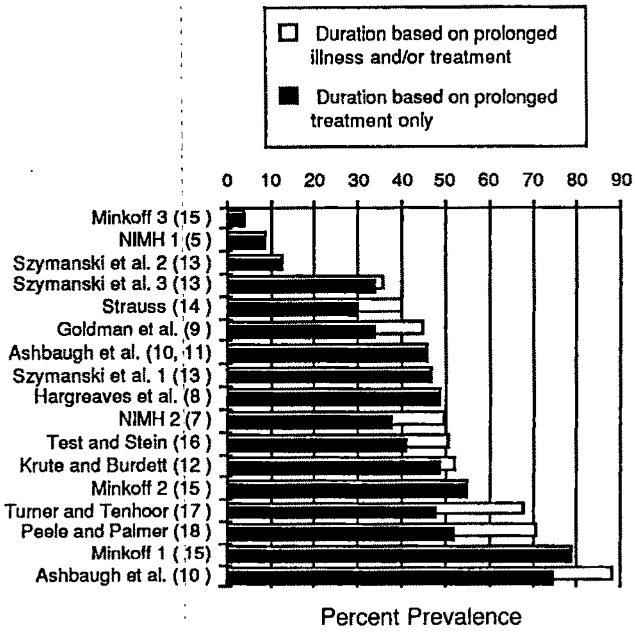
The variance in estimates based on the first criterion is considerable, ranging from a high of 79%–88% to a low of 4%–13%. The middle range falls between one-third and two-thirds (36%–71%). The NIMH 1987 definition (7) yields a 50% prevalence estimate, which we consider representative of the middle-range group.

High estimates of prevalence (79% to 88%) are due to the generality and all-inclusive nature of the definitions of Minkoff 1 (15) and Ashbaugh et al. (10) when applied to the West Philadelphia treated population. The Minkoff 1 definition (15) is based on diagnosis alone, while for the Ashbaugh et al. definition (10), minimal conditions for disability and duration are met by most of the patients in the sample.

Low prevalence estimates (4% to 40%) result when more stringent criteria are applied regarding repeated hospitalization (NIMH 1 [5] and Szymanski et al. 2 [13]), institutionalization (Minkoff 3 [15]), schizophrenia (Szymanski et al. 3 [13]), and patients whose disability reflects *both* social and work-related impairment (Strauss [14]).

Prevalence estimates of serious mental illness in the treated population drop by some 10% to 15% when only the treatment period (2 or more years) is used as a measure of illness duration (figure 1). For example, prevalence estimates based on the NIMH 1987 definition (7) drop from 50% to 38%, on Test and Stein (16) from 51% to 41%, and on Goldman et al. (9) from 45% to 34%. However, prevalence estimates based on Hargreaves et al. (8) remain at 49% and on Ashbaugh et al. (10, 11) at 46%, since their definitions do not depend on duration of service but rather on type and frequency of service utilization.

FIGURE 1. Estimates of Prevalence of Severe and Persistent Mental Illness in a West Philadelphia Sample (N=222)



The failure to use certain disability criteria in the analysis (i.e., vulnerability to stress and lack of self-sufficiency and independence) was due to the difficulty in interpreting and specifying them operationally. We do not believe that this had an impact on the results, since most of the information is captured by other criteria (i.e., impaired social functioning, employment, and activities of daily living were used to reflect vulnerability and lack of independence).

In order to study the consistency of the definitions identifying the seriously mentally ill, we selected the NIMH definition (7) as a reference against which all other definitions are compared. This is based on the assumption that the NIMH definition reflects a national perspective on severe and persistent mental illness. The comparison statistics for each definition (author), as shown in table 2, is the percent agreement with the NIMH 1987 definition (7) on 1) severely and persistently mentally ill patients and 2) nonsevere and persistent mentally ill patients. For example, 74% of the patients who were seriously mentally ill according to the NIMH 1987 definition (7) were selected by Hargreaves et al. (8), and 77% of the nonseriously ill patients were similarly defined by Hargreaves et al. (8).

As expected, definitions with high- or low-prevalence estimates were lower in their percent of agreement with the NIMH 1987 definition (7). The high-prevalence group (Minkoff 1 [15] and Ashbaugh et al. [10]) identified all of the seriously mentally ill patients as per NIMH (7) but differed substantially from NIMH (7) on the nonseriously mentally ill patients. The low-prevalence group (Minkoff 3 [15], NIMH 1 [5], and Szymanski et al. 2 [13]) easily identified most of the nonsevere and persistent mentally ill patients but

TABLE 2. Agreement With NIMH of Author Definitions of Severe and Persistent Mental Illness Applied to a West Philadelphia Sample (N=222)

	Agreement With NIMH on			
	Seriously Mentally Ill		Nonseriously Mentally Ill	
Author	N	%	N	%
NIMH 1 (5)	38	17	220	99
Krute et al. (12)	38	17	164	74
Minkoff 1 (15)	222	100	91	41
Minkoff 2 (15)	200	90	178	80
Minkoff 3 (15)	16	7	222	100
Test et al. (16)	209	94	202	91
Turner et al. (17)	222	100	144	65
Peele et al. (18)	211	95	118	53
Strauss (14)	160	72	204	92
Goldman et al. (9)	182	82	204	92
Szymanski et al. 1 (13)	135	61	149	67
Szymanski et al. 2 (13)	42	19	206	93
Szymanski et al. 3 (13)	113	51	175	79
Ashbaugh et al. (10)	222	100	51	23
Ashbaugh et al. (10, 11)	131	59	149	67
Hargreaves et al. (8)	164	74	171	77

TABLE 3. Sensitivity Analysis of the NIMH 1987 Definition of Severe and Persistent Mental Illness Applied to a West Philadelphia Sample (N=222)

	Specification[a]			Patients With Severe and Persistent Mental Illness	
Definition Criteria	Diagnosis	Disability	Duration	N	%
Diagnosis alone	x			167	75
Disability alone	—	≥1	—	206	93
	—	≥2	—	184	83
	—	≥3	—	153	69
	—	≥4	—	75	34
	—	≥5	—	13	6
Duration alone	—	—	x	193	87
Diagnosis and disability	x	≥3	—	120	54
Diagnosis and duration	x	—	x	149	67
Combinations of diagnosis, disability, duration	x	≥1	x	147	66
	x	≥2	x	133	60
	x	≥3	x	111	50
	x	≥4	x	62	28
	x	≥5	x	11	5

[a] An x or ≥=inclusive of a criterion in the definition of severe and persistent mental illness; digit following ≥=minimum number of disability categories.

greatly differed with NIMH on the severe and persistent mentally ill patients. The definitions of Test and Stein (16), Goldman et al. (9), Ashbaugh and Manderscheid (11), and Minkoff (15) offer prevalence estimates that are most consistent with those of NIMH (7).

Finally, table 3 provides a sensitivity analysis of our operationalization of the NIMH 1987 definition (7). Fourteen possible definitions are provided, each representing a different combination or number of elements within the three criteria. Each row in table 3 refers to a different variant of the NIMH definition. For example, the first row refers to a definition based only on diagnosis, the 8th row combines diagnosis and at least three of the disability categories listed in table 1, and the 12th row represents the implementation of the NIMH definition as it appears in table 1. Diagnosis and duration alone (row 9) provide a prevalence estimate of 67%. In our sample of a treated population, these two criteria are sufficient indicators of some degree of disability or dysfunction. This may also be true for a more general population because of the high coincidence and redundancy of the three criteria. A substantial reduction in prevalence to 50% is realized only after three of the disability categories are added (NIMH [7]).

CONCLUSIONS

The analysis in this paper reveals a large variance in prevalence estimates of severe and persistent mental illness resulting from differences in definitions. We found many prevalence estimates sensitive to the way in which the definitions were operationalized, for example, whether duration is based on persistence of illness or treatment period, whether disability is determined by moderate or marked impairment. The differences in prevalence exist despite the consistency in the implementation procedure used across definitions and the common sample of treated population used for all estimates. We expect, therefore, that as definitions of the seriously mentally ill continue to vary across communities, so will the beneficiaries of programs designed to serve this population. Unless consensus can be reached on a framework for defining serious mental illness, treatment will depend more on the community where one resides than on the severity of mental illness (25).

On July 23–24, 1987, the NIMH Division of Biometry and Applied Science convened a workgroup to develop a consensus definition of the seriously mentally ill for use by the clinical, policy, and research communities (1). Two brief papers by H.H. Goldman (unpublished paper, 1988) and Hargreaves (4), written pursuant to the meeting, outline the area of consensus achieved by the group as well as areas of possible disagreement. The papers report on conceptual clarity achieved in elucidating the dimensions of serious mental illness and on proposals to operationalize the definition using measures of disability or dysfunction that are congruent with the Social Security Administration's approach to defining disability. There is general consensus that the duration criterion should reflect the persistence of disability and not the duration of illness or treatment time. Hargreaves et al. (8) and Goldman et al. (9) also view prior service utilization, especially for schizophrenic patients, as a potential indicator of long-term disability that is worthy of further exploration. Bachrach (1) voices concern, however, that since the classification entails a forecast of the persistence of the patient's disability over some future period, prior service utilization (especially hospitalization) is a poor indicator of chronicity now that most patients reside in the community.

It is apparent from these reports that the "state of the art" definition of severe and persistent mental illness is still evolving. Consensus on diagnosis and disability seems to have coalesced, although departures from the consensus definition will and should occur within specific communities with special needs. The stumbling block seems to be duration of disability: is disability persistent or periodic? If persistent, how long a period before the illness becomes chronic? If periodic, how many recurrences of dysfunction constitute a chronic disability? There is also uncertainty as to whether chronicity should be defined with regard to duration of illness or disability or both and whether diagnosis, disability, and duration should be equally weighted or priority given to one criterion over another (1, 27, 28).

The research literature to date offers few clues as to how these questions might be resolved, and it is doubtful that continuous monitoring of a patient's diagnosis, level of dysfunction, and service outcomes is feasible in the community in the immediate future. Although many feel that patterns of service utilization are weak indicators of the level of dysfunction and chronicity, such data are readily available to most mental health systems, and research should be directed to establish whether patterns of prior and ongoing service utilization can serve as interim predictors of severe and persistent mental illness.

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Brainstem Auditory Evoked Response and Subcortical Abnormalities in Autism

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Previous studies of the neurobiology of autism that have used the brainstem auditory evoked response have given contradictory results. The authors of this study considered two supplementary aspects; they added an ipsilateral masking procedure, and they compared the results for every subject to the values (corrected for age and sex) of a large number of normal children. Twenty autistic (according to DSM-III-R *criteria) and 13 mentally retarded (nonverbal IQ <75) subjects were assessed. Eighty percent of the autistic subjects had abnormal interpeak latencies, compared to 15% of the mentally retarded subjects. The I–V and III–V prolonged interpeak latency values were seen only in the autistic subjects. The ipsilateral masking procedure doubled the rate of detection of higher-brainstem abnormalities in the autistic children.*

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We do not know the neurobiology of autism. The rationale for the use of brainstem auditory evoked response (BAER) as a probe in autism is that it provides a noninvasive technique for assessing what goes on in parts of the brainstem, a structure that shows evidence of impairment in some autistic persons (1–4). As Courchesne (5) put it, looking at the neural responses to specific pieces of information delivered to an autistic person can help us understand what the nervous system does to information in autism, and within this context the auditory evoked potentials are a rapidly evolving and promising field of investigation (6). The use of BAER as a probe technique in samples of autistic patients has produced contradictory results. The results of the first study to report prolonged interpeak latencies (7) were amended and reported to be weaker, after a few months, by the same group that had described them (8). Since then, many studies have shown such abnormalities (9–14), and a few have not (15, 16). Rumsey et al. (17) suggested that abnormal interpeak latencies could be secondary to 1) identifiable neurological diseases and auditory sensory deficits in autistic children, 2) inadequately matched control groups, 3) a high level of artifacts in the recordings, or 4) poor reliability of the measure.

Because of the importance of identifying the neurobiological factors in autism, we decided to try to further clarify these issues. Our study differed from those already reported in several ways: we added an unusual method of recording (ipsilateral noise), and we used an extensive normative database for children (18).

METHOD

Our sample was recruited either from the clinical population of the department of psychiatry at the Hôtel-Dieu du Sacré-Coeur de Jésus or through the cooperation of the parents of the Société Québécoise de l'Autisme. The Hôtel-Dieu du Sacré-Coeur is the child and adolescent mental health center of our area, providing inpatient and outpatient services to the catchment area of eastern Quebec. Each child in this study was known and had been previously diagnosed by one of the 18 child psychiatrists in our locality. The diagnostic criteria in use are those of *DSM-III-R.*

The principal investigator (J.T.) met all the referred patients and their parents to form a second diagnostic opinion. In addition, a psychologist working on our team (C.B.) met all the parents to complete a questionnaire related to autism according to *DSM-III-R* and also the Vineland Adaptive Behavior Scales (19) whenever necessary. There was perfect agreement on the diagnoses of all the patients in the sample, except for one patient whose diagnosis of mental retardation versus receptive dysphasia was disputed; this case was not

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retained for the analysis. Special attention was given to the differential diagnosis between autism and receptive dysphasia (20, 21). Because three of four autistic children are mentally retarded (22), we included a comparison group of children whose mental retardation was not associated with autism. Given the degree of mental retardation of most of our autistic subjects, it was not possible to test them on the WISC-R. Consequently, the Vineland Adaptive Behavior Scales (19) were used for measuring adaptive behavior, which is closely linked in both theory and practice to the concept of mental retardation (23). The mean±SD total scores on those scales for the autistic and mentally retarded groups were 51.5±23.3 and 64.0±15.5, respectively. The results we report here were observed in a sample of 20 autistic subjects (13 male and seven female; mean±SD age=10.6±5.1 years, range=5–26) and 13 mentally retarded children (nine male and four female; mean age=8.9±3.6 years, range=5–15). We retained only two exclusionary criteria: absence of wave components and presence of a known neurological disease that directly implicates the brainstem or auditory nerve. From all the available information, there were no striking differences between the autistic and mentally retarded groups with respect to the presence of mental retardation, associated neurological disorders, and peripheral hearing deficits.

The recordings were made in a soundproof Faraday cage. Eleven of the 33 subjects were sedated with chlorpromazine whenever necessary. It has been shown that BAER characteristics are not altered in persons receiving therapeutic or even toxic doses of major tranquilizers (24). The main recording and reference sites were Cz and the ipsilateral mastoid. We used unfiltered rarefaction clicks (100 μsec) in both right and left monaural stimulation (TDH-39 earphones) at a rate of 11.1 clicks per second for 2,000 sweeps on the test and the retest. When possible, the auditory threshold of the child was determined and a 70-dB (SL) level was used; the threshold could be determined in four autistic and four mentally retarded children. (This low number was due to the lack of cooperation of these mentally retarded children.) In the other cases, the apparatus was set at 78 dB, which represents the mean setting on our equipment relative to a level of 70 dB (SL) in a group of 177 normal children. We used a simultaneous contralateral masking noise of 30 dB less than the intensity of the click in the ipsilateral ear.

In addition to the regular recording procedure, we made recordings with an ipsilateral white noise of 30 dB less than the intensity of the stimulating clicks. Squires and Hecox (25) showed the usefulness of recording with ipsilateral masking in a patient with verbal auditory decoding difficulty. In this particular patient, the use of the ipsilateral masking procedure, which led to a disappearance of the middle and late auditory evoked components, neurophysiologically mimicked, so to speak, the decoding difficulties she reported under conditions of background noise in her daily life. We thought that because young children are not as sophisticated as adults in reporting their symptoms, many language-impaired children could present the same clinical and electrophysiological characteristics. Furthermore, we thought that if the ipsilateral masking method led to such large alterations in the later auditory components, it could possibly show small detectable effects on early components (brainstem) as well in our patients. For this reason, while working with language-impaired children, we had previously done ipsilateral masking recordings of 124 normal children to establish appropriate norms.

TABLE 1. Percentage of Explained Variance Among Latency Values (Spearman Correlation Coefficients of Left-Ear Values) in Brainstem Auditory Evoked Responses of 177 Normal Children

Wave Group	Wave I	Wave II	Wave III	Wave IV	Wave V
I–III	8^a	12^a	55^a	13^a	10^a
I–V	3^b	4^a	13^a	26^a	70^a
III–V	0	1	5^a	8^a	44^a

^{a}p<0.01.
^{b}p<0.05.

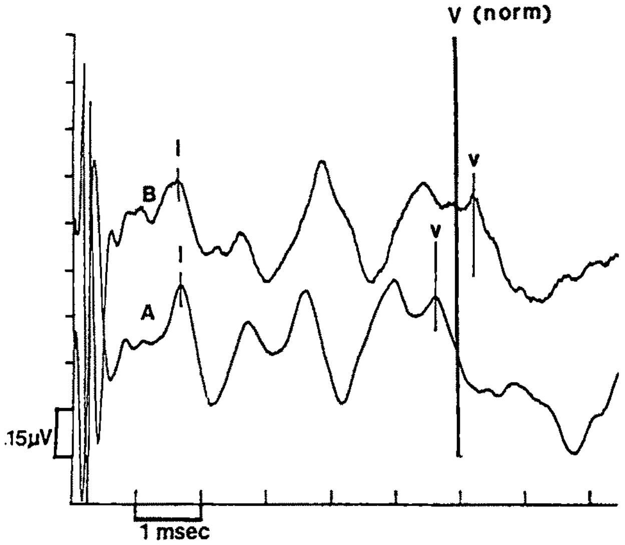
Wave I of the BAER represents the action potential of the acoustic nerve; however, we do not have such precise knowledge about the generators of the subsequent components, although we have fairly clear evidence that wave III originates from brainstem structures lower than those for wave V (26–28). Moreover, in our previous study of 177 normal children (29), our correlation studies clearly established (see table 1) that the variation for our three interpeak latency values came mainly from the variation of the most distal component (i.e., wave III for I–III, wave V for I–V, wave V for III–V). For this reason, in the present analysis, we considered waves III–V and I–V to belong to the same set, thus subdividing our interpeak latency abnormalities into low-brainstem (I–III) and high-brainstem (III–V and I–V) groups. The record of every child in our two groups was compared to the appropriate normative values of our laboratory. These values take into account the influence of age and sex on the components (13, 18), and we arbitrarily set our normality cutoff point at 2.5 standard deviations.

The project was explained to the parents, who signed consent forms.

RESULTS

All of the main components (waves I, III, and V) were clearly identifiable, according to the test-retest criteria, for every one of our subjects (see figure 1); i.e., whenever a component was identified at a given latency value in the test, it was also identified at the same latency value ±0.04 msec in the retest. Table 2 indicates that 80% of the autistic children showed an abnormal increase of some interpeak latencies, compared to 15% of the children with mental retardation. Table 2 also shows that increased wave III–V and I–V inter-

FIGURE 1. Brainstem Auditory Evoked Response Waveforms of a Normal and an Autistic Boy[a]



[a]Thick line labeled V (norm) indicates the upper limit of the norm at 2.5 standard deviations for the latency of wave V, as calculated from a group of normal boys, when the method without ipsilateral masking was used. A=waveform of a 5-year-old normal boy; B=waveform of a 5-year-old autistic boy. I=wave I; V=wave V.

TABLE 2. Autistic and Mentally Retarded Subjects Showing Prolonged Interpeak Latencies in Brainstem Auditory Evoked Response[a]

Group	Subjects in Whom Abnormality Was Detected Without Ipsilateral Masking	Subjects in Whom Abnormality Was Detected With Ipsilateral Masking	Total N	Total %
Autistic subjects (N=20)				
Without abnormality	—	—	4	20
With abnormality[b]	—	—	16	80[c]
Lower brainstem (waves I–III)	8	5	8	50
Higher brainstem	—	—	10	62
Waves III–V	2	3	5	31
Waves I–V	4	3	7	44
Mentally retarded subjects (N=13)				
Without abnormality	—	—	11	85
With abnormality	—	—	2	15[c]
Lower brainstem (waves I–III)	1	1	2	100
Higher brainstem	—	—	0	0
Waves III–V	0	0	0	0
Waves I–V	0	0	0	0

[a]Every interpeak latency value of every subject was measured against the appropriate norm for his or her age and/or sex (see reference 17).

[b]The numbers in this section do not add up to 16 because two subjects showed some lower-brainstem abnormalities associated with some higher-brainstem abnormalities; one subject, under both conditions (without and with ipsilateral masking), simultaneously presented both types of higher-brainstem abnormalities, that is, waves III–V and I–V.

[c]Significant difference between autistic and mentally retarded groups ($G^2=11.46$, df=1, $p<0.001$, likelihood ratio test).

peak latencies occurred only in the autistic group, with no representation in the retarded group. When added to the procedure without masking, the ipsilateral masking procedure doubled the rate of detection of higher-brainstem abnormalities in our autistic group, which is in contrast to what one observes with lower-brainstem abnormalities.

The high proportion of interpeak latency abnormalities in our sample of autistic children in striking. In order to compare our study to all of those that have used a recording procedure without ipsilateral masking, we excluded the results we obtained with ipsilateral masking. Table 3 shows the number of autistic subjects with wave I–V and III–V interpeak latency abnormalities, when the standard method (without ipsilateral masking) was used, across all the studies for which the information is available. The average percentage for all of those studies is 25%, which is about the same percentage we found in the present study under comparable conditions. Therefore, one major factor that seems to account for our finding such a level of higher-brainstem abnormalities is our applying the ipsilateral masking procedure in recording.

A few years ago, R.J. McClelland et al. (unpublished paper, 1986) suggested that some BAER anomalies could be related to age in autistic subjects. They reported normal wave I–V interpeak latency values in their autistic subjects under the age of 15 and abnormally prolonged values in the majority of the autistic subjects over age 15. They also reported that a control group of nonautistic retarded children matched for age and sex had normal values, which is in total agreement with our own observations. Looking at our data from the age perspective, we observed that four of the five subjects showing abnormalities with the usual recording procedure (without ipsilateral masking) were over the age of 14 (26 years, 15 years [N=3], and 9 years), which is similar to McClelland et al.'s observations. Furthermore, all of the children for whom the ipsilateral masking procedure elicited abnormalities were under 14 years of age (4, 5, 8, 12, and 13 years). Our small number precludes any strong conclusion, but this might suggest an age-relatedness depending on the method used, that is, with or without masking.

DISCUSSION

We find it interesting that our data tend to support some degree of independence between our empirically derived categorizations of higher-brainstem and lower-brainstem abnormalities (table 3): only a small number of subjects (two of 16) showed both higher- and lower-brainstem abnormalities simultaneously. Moreover, in the comparisons of the stimulations with versus without ipsilateral masking for every subject, two facts

TABLE 3. Prolonged Interpeak Latencies in Brainstem Auditory Evoked Responses of Autistic Patients Across Studies

Study	N	Number of Patients With Higher-Brainstem Abnormalities	Number of Patients With Higher- and Lower-Brainstem Abnormalities	Diagnostic Criteria for Autism
Student & Sohmer (7)	15	—	—	Creak
Rosenblum et al. (9)	6	—	—	NSAC[a]
Novick et al. (30)	5	1	1	—
Skoff et al. (10)	14	5	8	—
Taylor et al. (12)	32	—	—	NSAC[a]
Tanguay et al. (13)	14	4	6	*DSM-III*
Gilberg et al. (31)	24	8	8	Rutter
Rumsey et al. (17)	25	1	1	*DSM-III*
Courchesne et al. (16)	14	0	0	*DSM-III*
Skoff et al. (11)	26	6	6	—
McClelland et al. (unpublished, 1986)	20	10	10	Rutter
Thivierge & Côté (18)	21	5	12[b]	*DSM-III-R*
All studies	163[c]	40 (25%)	52 (32%)	—

[a] National Society for Autistic Children (1977).
[b] Without ipsilateral masking.
[c] Total for all the studies in which higher- and lower-brainstem abnormalities were reported.

emerged: a concordance of results for the wave I–III abnormality (i.e., when a subject shows lower-brainstem abnormality without masking, he or she also shows it with masking) and a discordance of results for the wave I–V and III–V abnormalities (i.e., when a subject shows higher-brainstem abnormality without masking, he or she does not show it with ipsilateral masking). Lower- and higher-brainstem abnormalities seem to behave differently under both conditions of recording, which could be an expression of different physiological underpinnings.

In speculating on the neurobiological aspects of interpeak latency findings, it must be noted that BAER is classically described as more sensitive to white matter than to gray matter diseases involving the brainstem (32). However, studying patients with renal failure before and after dialysis, Pratt et al. (33) provided evidence that calcium level may be an important factor influencing BAER values: the lower the calcium level, the greater the BAER absolute latency and interpeak latency values. Calcium is known to be involved in synaptic transmission, and abnormally low levels of calcium have been described in autistic subjects (34, 35). Within this context, it is tempting to offer the speculation that prolonged interpeak latencies might possibly constitute an index of synaptic inefficiency in the brainstem of autistic persons, this possibility being related to low calcium levels.

Given the few but consistent indications (36–39) that the effect of masking on the more distal BAER components could be of CNS origin, one could take our ipsilateral masking results as possibly indicative of a central dysfunction in some autistic subjects. If one speculates further on why the ipsilateral masking procedure doubles the detection rate of interpeak latency abnormalities, one immediately thinks of this fact as being related to the subjects' age; it could indicate a faulty maturational process which, in young autistic children, only shows up under ipsilateral masking.

Both prolongation and shortening of interpeak latency have been reported in autism (13, 17). In the present study, we were mostly interested in an index whose interpretation was less ambiguous from the standpoint of neurobiology. This is why we concentrated our analysis on prolonged interpeak latency. A comparison between the 16 autistic children who showed prolonged interpeak latency and the four who did not was done from the standpoint of the available clinical, psychometric, and neuropathological variables, and no striking differences emerged.

Differences among studies can rightly be ascribed to methodological differences such as the diagnostic criteria used, rate of stimulation, and norms derived from a small number of subjects. One methodological advantage of the present study is that it relied on norms derived from a fairly large number of normal children for both procedures (with and without ipsilateral masking) and also on norms that take into account the influence of age and sex on the different components (18).

The fact that many autistic children have normal BAER indicates that BAER abnormalities are not related to autism, as defined by any present set of criteria (table 3), as a necessary condition. This could be because impairment of the nervous structures under scrutiny is not essential for autism to develop; but it could also be because of the inconsistencies and heterogeneity of our diagnostic criteria or because our present investigative tools are rudimentary. The present results are interpreted as suggesting that the use of BAER both with and without masking procedures might help us identify a dysfunctional maturational process in the higher brainstem of 50% of autistic subjects who are diagnosed according to *DSM-III-R* criteria and that this dysfunctional process is not related to the concomitant mental retardation of the subjects.

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The UCLA-University of Utah Epidemiologic Survey of Autism: The Etiologic Role of Rare Diseases

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Twelve rare diseases known to cause CNS pathology were found in 26 (11%) of 233 autistic probands identified during a recent epidemiologic survey of Utah. These 26 probands had significantly lower mean IQs than the remaining patients (43 versus 60) but similar sex distribution and prevalence of abnormal EEGs and seizures. The rarity and diversity of these 12 diseases make it highly unlikely that they randomly occurred with autism. Their presence in this epidemiologic survey is the most compelling evidence to date to support the hypothesis that different diseases producing different types of CNS pathology can play an etiologic role in autism.

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Autism is a behaviorally defined syndrome (*DSM-III, DSM-III-R*) (1, 2). It is usually diagnosed before 3 years of age by the appearance of characteristic disturbances of developmental rates and sequences, language, relatedness, responses to sensory stimulus, and repetitive/stereotyped behaviors. While no specific pathognomonic signs or CNS pathology is known, biomedical findings have been reported that characterize subgroups of patients. These findings include hyperserotonemia (3), lower b-wave amplitude in the electroretinogram (4), lower postrotatory nystagmus (5), lower cerebellar Purkinje cell counts at autopsy (6), and nonspecific abnormal EEGs, magnetic resonance imaging (MRI) scans, CT scans, and pneumoencephalograms (1, 7–10).

The search for the cause of autism has focused on three major areas: genetics; potential pathological pre-, peri-, and postnatal factors; and concurrent diseases. Recent evidence from our epidemiologic survey of Utah (11–15) and other centers (see reference 16 for review) indicates that there are probably genetic factors which predispose certain families to have multiple cases of autism. The exact nature and type of genetic loading remain to be determined. Second, surveys of natal factors have failed to identify specific events or clusters of events that could account for individual cases or a subset of cases (17–21). We have conducted three such negative surveys (15, 22, 23), including a review of the medical records of 233 autistic patients identified in our epidemiologic survey of Utah (15).

The third area of exploration for possible etiologic agents, the identification of concurrent diseases that could cause CNS pathology, has been more rewarding. Appendix 1 contains a list of diseases, most of which are extremely rare, that have been reported to occur with autism (7–10, 24). Whether these diseases were randomly associated or causative of autism cannot be determined from case reports or clinical surveys because of the nonepidemiologic nature of the data. However, on the basis of a large number of observations from different centers throughout the world, a consensus has been reached that at certain stages three diseases can produce the clinical picture of autism. They are rubella encephalitis, Rett's syndrome, and fragile X syndrome.

In this report we present a solution to unraveling the problem of random co-occurrence versus etiologic significance. We report on diseases that were found to occur with autism during a complete epidemiologic survey of Utah, a state with a population of approximately 1.6 million.

METHOD

Our recent epidemiologic survey of autism in the state of Utah (11) employed a four-level ascertainment system, *DSM-III* criteria, and a team of highly experienced clinicians who conducted blind diagnostic evaluations throughout the state. A total of 489 possibly autistic individuals born between 1960 and 1984 and

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living in Utah during the survey (1984–1988) were ascertained, and 241 were diagnosed as autistic. They came from 195 single-incidence families and 20 multiple-incidence families. The latter contained a total of 46 autistic siblings. Genetic research shows no excess of inbreeding or consanguinity in Utah, and the gene pool is fully representative of North American and European Caucasian populations.

Medical records were available for 233 autistic subjects. The records were abstracted by one of the authors (A.M.-B.) directly onto an IBM R-Base computer system. Data were available on the following percentages of subjects: 99.6% (N=232), IQ tests; 67.8% (N=158), EEGs; 79.8% (N=186), obstetrical; 90.1% (N=210), birth; 87.6% (N=204), pediatric; 100% (N=233), diagnostic; and 98.3% (N=229), school records.

RESULTS

Twelve rare diseases known to produce CNS pathology and/or developmental delays occurred in the total population of 233 patients surveyed whose medical records were available out of the population of 241 (table 1). These diseases cause a variety of structural and functional pathology throughout the brain. Such diversity supports the hypothesis that various types of pathology occurring during early fetal life can produce the syndrome of autism.

Concurrent Diseases

Viral and bacterial infections. Of the total population (N=233), 2.6% (N=6) had congenital viral infections or suspected infections, and two males (0.9%) had hemophilus influenza meningitis. A patient with suspected congenital rubella had microphthalmia and roving nystagmus but no other stigmata of congenital rubella. Virus was not isolated at the patient's birth, and a subsequent antibody titer was 1:160. The patient had three sisters with the diagnosis of autism. A patient with congenital herpes had a second-born female co-twin who died at 12 days of age of congenital herpes. He had a severe hearing loss, scarring of the retina, and psychomotor seizures beginning at age 2. A second patient with congenital herpes had an abnormal EEG at age 20 months, no clinical seizures, and died at age 19 years of staphylococcus septicemia. One patient developed hemophilus influenza meningitis at 5 months at which time the virus was cultured from his spinal fluid. He had an older brother with a diagnosis of autism. Another patient had hemophilus influenza meningitis at 7 months, bilateral otitis media, frequent upper respiratory infections, recurrent fevers, anemia, and gastroenteritis. At 8 months he had a period of vomiting, diarrhea, and pneumonia. After these illnesses he was observed to be unaffectionate and rocked continually until 1½ years of age. Petit and grand mal seizures began when he was 7 months old. The mean IQ of the eight patients with viral and bacterial infections was 58.

Chromosome and genetic abnormalities. Eight males were screened for fragile X syndrome; two had the abnormality. Five males had trisomy 21, and one was not karyotyped. One male had a partial trisomy of the distal tip of chromosome 8 and a probable partial deletion of the middle of the short arm of chromosome 8. This trisomy is known to affect brain development, depending on the location of the duplication. To our knowledge, this association of autism and trisomy of chromosome 8 has not previously been reported (25). One male had a deletion of the short arm of chromosome 9 (26, 27). One female had a demonstrable translocation from the long arm of the chromosome 5 pair to a long arm of one of the chromosome 11 pair, a balanced reciprocal translocation. Her father also had this translocation. Except for one child with fragile X syndrome, one child with a deletion of the short arm of chromosome 9, and one with tuberous sclerosis (28), all children in this group were profoundly retarded, and no families had more than one autistic child. The mean IQ of the 11 patients in this group was 37. It is interesting to note that in the UCLA Genetic Registry (non-Utah), there is an autistic female with Down's syndrome, unkaryotyped, with an autistic older brother and a normal younger brother.

Metabolic disorders. Seven patients (four males, three females; sex ratio=1.33 to 1) had metabolic disturbances. Two siblings, one male (IQ=68) and one female (IQ=35) had mucopolysaccharidosis III, Sanfilippo's syndrome, type A. It is an enzyme deficiency of heparan N-sulfatase and is well-known to cause CNS pathology. Results of urine screens for these children were negative except in one case. Formal diagnosis was made by a skin fibroblast culture in the male sibling. Sanfilippo's syndrome, type A, has not been reported previously to be associated with autism; however, some patients with a diagnosis of autism are known to have the disease (E. Neufeld, personal communication). All patients with the stigmata of mucopolysaccharidosis should be screened by fibroblast cultures. One patient and his firstborn normal twin had a disaccharidase deficiency. They were hospitalized at 2 months of age for pneumonia, and both had recurrent bronchitis and otitis media, which was treated with polyethylene tubes.

Congenital hypothyroidism (sporadic cretinism) was diagnosed at 6 months in one female patient. She had a short, stocky appearance, puffy eyelids, short neck and thick tongue, open anterior fontanelle, sparse and dry hair, doughy and dry skin, protuberant abdomen with a large umbilical hernia, and tenacious mucous production. She was reported to have been a sleepy infant and a poor eater, had had a hoarse and persistent cry since birth, and had a bilirubin level of 0.9 mg/100 ml at 6 days. One male patient was given a diagnosis of congenital hypothyroidism (cretinism) at 7 months. He was jaundiced at 3 months (no bilirubin level was reported) and had retarded early develop-

TABLE 1. Concurrent Diseases Found in Autistic Patients in Utah Autism Survey

Category and Disease	N	Sex	IQ	Abnormal EEG/Seizures
Viral and bacterial infections (N=8)				
Congenital rubella[a]	1	M	56	—
Congenital rubella, possible[a]	1	M	83	—
Congenital cytomegalovirus[a]	1	M	36	—
Congenital herpes, possible[a]	1	M	28	—
Congenital herpes[a,b]	2	M	74	Psychomotor
		M	15	Abnormal EEG
Hemophilus influenza meningitis	2	M	69	Grand mal
		M	101	—
Chromosome and genetic abnormalities (N=12)				
Fragile X syndrome[a]	2	M	31	Petit and grand mal
		M	89	—
Down's syndrome, trisomy (chromosome 21)[a]	5	M	25	—
		M	31	—
		M	30	—
		M	25	—
		M	28	Myoclonic
Down's syndrome, unkaryotyped[a]	1	M	25	—
Trisomy (chromosome 8)[a]	1	M	36	—
Deletion (chromosome 9)[a]	1	M	60	—
Translocation (chromosome 5)	1	F	33	—
Tuberous sclerosis (chromosome 9)[a]	1	M	52	Febrile (on two occasions)
Metabolic disorders (N=7)				
Mucopolysaccharidosis III, Sanfilippo, type A[a,c]	2	F	35	—
		M	68	Febrile at birth
Disaccharidase deficiency	1	M	48	—
Diabetes, juvenile onset	1	F	17	—
Congenital hypothyroidism[a]	2	F	58	—
		M	69	—
Pituitary deficiency[a,d]	1	M	50	—
Congenital anomaly (N=1)				
Spina bifida, occulta	1	F	77	—
Related syndromes (N=6)				
Rett's syndrome[a]	4	F	18	—
		F	20	—
		F	25	Petit and grand mal
		F	31	Psychomotor
Tourette's syndrome	2	M	35	—
		M	115	—
Deafness (N=2)				
Recessive	1	F	60	—
Bilateral profound sensorineural	1	M	43	—
Eye disorders (N=3)				
Septo-optic dysplasia[d]	1	M	50	—
Atrophy of the optic nerve	1	M	75	Psychomotor
Retinitis pigmentosa[b]	1	M	28	—
Seizures (N=43)[e]				
Seizures	34	26 M, 8 F	51[f]	—
Febrile seizures	9	6 M, 3 F	59[f]	See tables 4 and 5

[a] Disease known to cause CNS pathology and/or developmental delay.
[b] One of the patients with congenital herpes also had retinitis pigmentosa.
[c] Siblings.
[d] The child with pituitary deficiency also had septo-optic dysplasia.
[e] A total of 189 subjects (151 males and 38 females) had no seizures; their mean IQ was 59 (IQ missing for one male).
[f] Mean IQ.

ment, constipation, dry skin, slow growth, lethargy, frequent upper respiratory infections, a very widely open fontanelle, and a large tongue. X-rays of his chest, spine, long bones, and skull were consistent with cretinism. Hypopituitarism was diagnosed shortly after birth in one male patient, and at 4 months septal-optic dysplasia was noted. This caused a lack of development of the optic nerve, with resulting blindness. The patient received thyroxine, hydrocortisone, and growth hormone supplementation. The mean IQ of the seven patients in this group was 49.

Congenital skeletal anomaly. Only one patient, a female (IQ=77), had a major skeletal anomaly, spina bifida occulta.

Related syndromes. Four females had symptoms of Rett's syndrome, and all were profoundly retarded. One developed petit mal seizures at 3 years and grand mal seizures at 4 years. She died at age 10 years. The

TABLE 2. IQ of Male and Female Autistic Subjects With and Without Concurrent Diseases in Utah Autism Survey

	Total[a,b] (N=232)			Males[b] (N=183)			Females[b] (N=49)		
		IQ			IQ			IQ	
Group	N	Mean	SD	N	Mean	SD	N	Mean	SD
No concurrent disease	195	59.9	26.0	156	62.5	26.2	39	49.6	23.1
Concurrent disease									
CNS disease	26	42.2	21.2	20	45.6	22.0	6	31.2	14.6
No CNS disease	11	61.2	29.9	7	69.4	30.1	4	46.8	26.9

[a] IQ missing for one male.

[b] Patients with concurrent CNS diseases had significantly lower mean IQs than the patients without concurrent diseases in the total sample ($t=3.89$, $df=35.9$, $p=0.0004$), among the males ($t=3.17$, $df=26.4$, $p=0.004$), and among the females ($t=2.63$, $df=9.4$, $p=0.03$).

TABLE 3. Relationship Between IQ and EEG, Seizures, and Type of Epilepsy in Autistic Subjects in Utah Autism Survey (N=232)[a]

	Total			Males			Females		
		IQ			IQ			IQ	
Item	N	Mean	SD	N	Mean	SD	N	Mean	SD
EEG results[b]									
Normal	103	57.4	26.4	77	62.4	26.7	26	42.8	19.3
Abnormal	55	51.7	23.7	42	52.8[b]	24.3	13	48.0	22.5
Seizures									
No seizures	189	59.4	26.6	151	62.5	26.6	38	47.1	23.0
Febrile seizures	9	58.9	27.9	6	57.8	34.3	3	61.0	12.8
Other seizures	34	51.0	23.7	26	53.7	22.9	8	42.3	25.4
Epilepsy type[c]									
Psychomotor	4	56.8	21.5	3	65.3	15.9	1	31.0	—
Myoclonic	—	—	—	2	23.5	6.4	—	—	—
Petit mal	—	—	—	4	48.8	24.5	—	—	—
Grand mal	24	52.7	24.3	17	56.3	22.9	7	43.9	27.0
Febrile	9	58.9	27.9	6	57.8	34.3	3	61.0	12.8

[a] IQ missing for one male.

[b] Males with abnormal EEGs had a significantly lower mean IQ than those with normal EEGs ($t=1.98$, $df=91.5$, $p=0.05$).

[c] Sample size too small for meaningful analysis.

cause of death was unknown, but it was thought to be due to a seizure. She had a female second cousin with autism but not Rett's syndrome. They were related through their mothers. A second female (IQ=31) developed psychomotor seizures at 2 years; her EEG was normal. The mean IQ for the four Rett's syndrome patients was 24 and for the two Tourette's syndrome patients, 75.

Deafness. One female (IQ=60) had a recessive type of deafness. Her younger sister was deaf but otherwise normal, and her mother had a hearing loss. One male had a bilateral profound sensorineural hearing loss. The mean IQ for these two patients was 52.

Eye disorders. One male (IQ=50) had septo-optic dysplasia, optic nerve atrophy, and a pituitary deficiency. A second male (IQ=75) had rod vision but lack of cone vision, atrophy of the optic nerve, hypoplastic optic discs, and nystagmus; he can read large print. A third male (IQ=28) had retinitis pigmentosa and congenital herpes and died at age 19 years of staphylococcus septicemia. The mean IQ of the three patients in this group was 51.

Concurrent diseases and IQ. The mean IQs of all patients with concurrent diseases are summarized in table 2. Concurrent diseases were divided into two groups—those which are known to cause CNS pathology and those which are not. The third group comprises the remaining patients without concurrent disorders. We calculated t tests to compare the mean IQs for each group (table 2). As shown, the patients with concurrent/CNS diseases had significantly lower mean IQs than the group without concurrent diseases. However, generalizations from these data are limited because of the small sample size. Similar results were obtained for the comparisons of concurrent/CNS diseases versus concurrent/non-CNS diseases, but these differences did not reach significant levels.

Seizures, EEGs, and age at onset. Table 3 presents data on the number of patients with seizures, their sex, and mean IQs. The only significant difference found was that males with abnormal EEGs had significantly ($p=0.05$) lower mean IQs than those with normal EEGs. This finding probably reflects the fact that so many analyses were done that it occurred by chance, since it has no apparent clinical significance. Table 4 contains individual data on sex, IQ, seizure type, age at onset, abnormal EEGs, and type of concurrent diseases. Table 5 shows the distribution of seizures and EEG abnormalities in the Utah autism survey. Fourteen patients with nonfebrile seizures (41.2%) developed them within the first 12 months of life, seven (20.6%) from 1 to 2 years, five (14.7%) from 2 to 3

TABLE 4. Abnormal EEGs and/or Epilepsy in Autistic Subjects in Utah Autism Survey

Patient	Sex	IQ	Seizure Type	Abnormal EEG	Age at Onset[a]	Concurrent Diseases
1	F	16	Petit and grand mal	Yes	4 months	—
2	F	20	Petit and grand mal	Yes	4 years	—
3[b]	F	25	Petit mal	Yes	3 years	Rett's syndrome
			Grand mal	Yes	4 years	—
4	F	31	Psychomotor	No	2 years	Rett's syndrome
5	F	37	Petit mal	Yes	10 months	—
			Grand mal	Yes	12 months	
6	F	41	None	Yes	8 years	—
7	F	50	Grand mal	Yes	6 months	—
8	F	50	None	Yes	6 years	—
9	F	50	Febrile (one occasion)	Yes	15 months	—
10	F	58	Febrile	No	12 months	—
11	F	70	None	Yes	—	—
12	F	74	Grand mal	Yes	8 days	Diabetes
13	F	75	Febrile	Yes	2 years	—
14	F	85	Grand mal	Yes	2 years	Associated with otitis media
15[b]	M	15	None	Yes	20 months	Congenital herpes, retinitis pigmentosa
16[b]	M	19	Myoclonic	Yes	5 days	—
			Postictal paralysis		3 months	
17	M	19	None	Yes	—	—
18	M	19	Petit mal	Yes	4 years	—
19	M	20	None	Yes	4 years	—
20	M	21	Febrile	Yes	2 months	—
21	M	21	Tonic-clonic	Yes	13 years	—
22	M	24	Febrile (four occasions)	Yes	2 years	—
23	M	25	Petit mal	Yes	3 years	—
			Grand mal		7 years	
24	M	28	Myoclonic	Yes	4 months	Trisomy (chromosome 21)
25	M	34	Petit and grand mal	Yes	12 months	Associated with fevers
26	M	31	Petit mal	Yes	18 months	Fragile X syndrome
			Grand mal		2 years	
27	M	38	None	Yes	3 years	—
28	M	39	Grand mal	Yes	13 years	—
29	M	40	None	Yes	7 years	—
30	M	40	Petit and grand mal	Yes	2 years	—
31	M	45	Petit and grand mal	Yes	4 years	—
32	M	47	Psychomotor	No	4 years	—
33	M	47	Tonic-clonic	Yes	6 years	—
			Grand mal		7 years	
34	M	47	None	Yes	3 years	—
35	M	47	Petit mal	Yes	5 months	Associated with otitis media
36	M	48	None	Yes	4 years	—
37	M	50	Petit mal	Yes	2 years	—
38	M	52	Febrile (two occasions)	Yes	18 months	Tuberous sclerosis
39	M	55	None	Yes	5 years	—
40	M	59	Idiopathic	Yes	6 months	—
41	M	65	None	Yes	6 years	—
42	M	66	None	Yes	4 years	—
43	M	67	None	Yes	5 years	—
44	M	67	None	Yes	3 years	—
45	M	68	Grand mal	Yes	15 months	—
46	M	68	Febrile	No	Birth	Sanfilippo's syndrome
47	M	68	Febrile	No	18 months	—
48	M	69	Petit and grand mal	Yes	7 months	Hemophilus influenza meningitis
49	M	69	Petit and grand mal	Yes	3 years	—
50	M	74	Psychomotor	Yes	2 years	Congenital herpes
51	M	75	Petit and grand mal	Yes	Birth	—
52	M	75	Psychomotor	Yes	4 years	Optic nerve atrophy
53	M	75	Idiopathic	Yes	34 months	Associated with otitis media
54	M	76	Petit and grand mal	Yes[c]	3 years	—
55	M	79	Petit mal	Yes	11 months	—
56	M	80	None	Yes	5 years	—
57	M	80	None	Yes	16 years	—
58	M	83	None—convulsions	Yes	5 years	—
59	M	84	Grand mal	No	8 months	—
60	M	92	None	Yes	4 years	—
61	M	100	Petit mal	No	3 years	—
			Grand mal		8 years	
62	M	114	Febrile	Yes	17 months	—

[a] Onset of seizures or EEG abnormalities. [b] Deceased. [c] EEG normal at 8 years.

TABLE 5. EEGs and Seizures in 233 Autistic Subjects in Utah Autism Survey

Seizure Status	N	%
No seizures	190	81.6
Normal EEG	96	41.2
Abnormal EEG	19	8.2
No EEG reported	75	32.2
Febrile seizures	9	3.9
Abnormal EEG	6	2.6
Normal EEG	3	1.3
Other seizures	34	14.6
Abnormal EEG	30	12.9
Normal EEG	4	1.7

years, five (14.7%) from 3 to 4 years, one (2.9%) from 5 to 10 years, and two (5.9%) after 10 years. Thus, a total of 41.2% developed seizures within the first year and 76.4% by the third year of life. In the febrile seizure group, two (22.2%) developed these seizures in the first 12 months of life, seven (77.8%) in the second 12 months, and none thereafter. In subjects with no seizures, an abnormal EEG was found for one patient (5.9%) from age 1 to 2 years, three (17.6%) from 2 to 3 years, four (23.5%) from 3 to 4 years, eight (47.1%) from 5 to 10 years, and one (5.9%) after age 10 years. For two patients the ages at EEG testing were unknown.

Families With Multiple Incidences of Autism

The proportion of patients from families with multiple incidences of autism who had abnormal EEGs (N=8, 30%) was similar to the proportion from families with single incidences of autism (N=47, 36%) (χ^2=0.05, df=1, p>0.80). Similarly, the proportion of patients from families with multiple incidences of autism who had nonfebrile seizures (N=4, 9%) was similar to the proportion from families with single incidences of autism (N=30, 16%) (χ^2=0.61, df=1, p>0.40).

Three patients with concurrent diseases known to cause CNS pathology (two with Sanfilippo's syndrome and one with possible rubella encephalitis) came from two families with multiple incidences of autism. The brother and sister with Sanfilippo's syndrome obviously are examples of the inheritance of a metabolic abnormality that probably produced autism. In the other family, the boy with possible rubella had three female siblings with autism but no rubella.

Probability of Occurrence of Other Diseases With Autism

The 12 diseases affecting the CNS that were identified in the survey are extremely rare. The most frequent is probably Down's syndrome, the prevalence of which is estimated to be 1 in 800 (29); the most rare is probably Sanfilippo's syndrome, estimated to occur with a prevalence of 1 in 24,000 (30). Comparably accurate prevalence estimates on the other diseases listed in table 1 are not available. However, clinical experience indicates that they occur less frequently than autism itself, which occurred in our population with a prevalence of four in 10,000. On the basis of these figures, the odds of Down's syndrome occurring with autism are approximately 4 in 8 million (1 in 800×4 in 10,000). The odds for the co-occurrence of the other diseases, assuming that they have the same prevalence as autism (this is a conservative estimate), are 16 in one hundred million (4 in 10,000×4 in 10,000), a truly astronomical number.

DISCUSSION

The results of our epidemiologic survey clearly indicate that the characteristic developmental delays and symptoms by which we diagnose autism can be directly caused by a variety of diseases that affect the CNS by different means. This conclusion must remain inferential, however, since direct neuropathological evidence is not available from epidemiologic data. However, it is to be hoped that these new epidemiologic data will sharpen the focus of further research and prevent further exploration of fruitless directions.

If one can generalize from the present data, it now appears prudent to assume that at least 11% of otherwise unselected subjects with autism that come to clinical attention will have concurrent diseases which cause the syndrome. The actual figure is probably larger, since we were unable to screen all probands for fragile X syndrome. However, the consensus of other recent surveys is that approximately 7% of otherwise unselected populations of autistic patients have fragile X syndrome (24). Projecting from this figure, we would have expected to have identified 16 patients with fragile X syndrome (7% of 233). However, only two were identified. If the 14 possibly missing cases of fragile X syndrome had been found among only the patients with nonconcurrent CNS diseases, then a total of 40 patients with concurrent diseases that affect the CNS would have been identified. Thus, instead of approximately 11% of the total population falling into this category, the figure would have risen to 17% (40 of 233). These estimated figures are given only for purposes of illustration.

It is interesting to note that the 26 patients with concurrent diseases known to affect the CNS were indistinguishable from the remaining patients on clinical grounds, with one exception, namely that they had lower mean IQs. Their sex ratio, EEGs, seizure histories, and general clinical picture were otherwise quite similar. This explains why these patients had not emerged as a separate subgroup in previously nonepidemiologic surveys or in surveys of specific clinical populations (31).

The overall rate of nonfebrile seizures was 14.6% (N=34). This is consistent with previous reports (32). It is of clinical interest to note that the mean IQ of patients with seizures was not significantly different

TABLE 6. Data on Deceased Probands in Utah Autism Survey

Patient	Age at Time of Death (years)	Sex	IQ	Concurrent Disorders	Cause of Death
1	19	M	15	Abnormal EEG, congenital herpes, retinitis pigmentosa	Staphylococcus septicemia
2	10	F	25	Rett's syndrome, petit and grand mal seizures	Unknown; possible seizures
3	19	M	35	None	Died in fire
4	7	M	29	Acute lymphocytic leukemia	Acute lymphocytic leukemia
5	10	M	19	Myoclonic seizures since 5 days of age and grand mal seizures	Unknown; acute pulmonary edema and congestion found at autopsy

from that of patients without seizures and that the mean age at onset of seizures was lower than reported in some prior series (32).

Five patients died during the 3 years of our survey (table 6). Two of these had concurrent diseases that affect the CNS (herpes and Rett's syndrome). This small number is consistent with the general clinical impression that autistic patients have normal longevity.

The primary diseases that cause CNS pathology are easily diagnosed by their characteristic clinical courses, signs, and symptoms, as was the case in our survey. This knowledge allows us to reduce "diagnostic fishing expeditions" and their cost and discomfort to our patients. More specifically, in practice we do not recommend extensive medical, neurological, and diagnostic workups on patients who have autism and no other clinical signs or symptoms of a concurrent disease.

In conclusion, the high probability against random co-occurrence of autism and other diseases is the best evidence to date to support the hypothesis that certain rare diseases that occurred in our population caused CNS pathology which, in turn, produced autism. That these diseases cause CNS pathology in different ways supports the hypothesis that the symptoms indicative of autism represent the final common pathway of various etiologic agents.

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APPENDIX 1. Diseases That Have Been Reported to Occur With Autism

Viral, Bacterial, and Parasitic Infections

- Rubella
- Cytomegalovirus
- Herpes
- Varicella
- Rubeola
- Toxoplasmosis
- Syphilis (lues)
- Mumps
- Hemophilus influenza

Chromosome and Genetic Abnormalities

- Fragile-X
- Down's syndrome (trisomy 21)
- Sex chromosome aneuploidy (XXX, XXY, XYY, XXYY)
- Autosomal abnormalities of chromosomes 1, 2, 3, 5, 6, 9, 13, 16, 17, 22
- Oculocutaneous albinism
- Tuberous sclerosis (chromosome 9)
- Neurofibromatosis (chromosome 17)
- Retinoblastoma (chromosome 13)

Metabolic Diseases

- Phenylketonuria
- Hyperlactatemia
- Histidinemia
- Lipidosis
- Addison's disease
- Hyperuricosuria
- Hurler's syndrome
- Hyper- and hypothyroidism
- Celiac disease
- Adrenoleukodystrophy
- Purine metabolism

Congenital Diseases

- Microcephaly
- Hydrocephalus
- Moebius syndrome
- Dandy-Walker syndrome
- Cornelia de Lange syndrome

Related diseases

- Rett's syndrome
- Tourette's syndrome

Other Diseases

- Lead ingestion
- Infantile spasms
- Vascular occlusion

Effects of Pill-Giving on Maintenance of Placebo Response in Patients With Chronic Mild Depression

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Fifty outpatients with mild, chronic, mood-reactive depression whose mood improved markedly after a 10-day single-blind placebo trial were randomly assigned in a double-blind design either to have their placebo medication discontinued or to have it maintained for an additional 6 weeks. Half of the patients in each condition relapsed within 6 weeks, indicating that pill-taking itself does not influence maintenance of placebo response. Placebo response was more likely to be maintained in patients who were currently married. At the end of 3 months, the overall relapse rate was 58%. The authors raise questions about the utility of the initial 10-day placebo washout in antidepressant clinical trials, and they discuss limits on the generalizability of their findings.

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The phenomenon of placebo response has been recognized for years, and many explanatory mechanisms have been proposed. In their review of "concepts of placebogenesis," Shapiro and Morris (1) listed 15 possible contributory factors. Those most salient to clinical antidepressant trials include expectancy effects, which influence the hope, faith, and morale of the patient (2); operant conditioning, in which contacts with the treatment staff and setting serve as reinforcers (3); persuasion and suggestibility; and the effects of the social influences inherent in pill-taking and the authority of the physician (4). Other processes, such as spontaneous improvement, patients' taking the initiative, possible therapeutic benefits of repeated assessments, and response bias (the desire of the patients at initial evaluation to convince the rater of their need for treatment and/or their desire to please the doctor by getting better) also may play a role in placebo response.

In previous work (5), depressed patients who were responders to 6 weeks of placebo administration were found more likely to be mood reactive and to have milder pretreatment symptoms than placebo nonresponders. In addition, in a previous comparison of 94 responders to 10 days of placebo administration and 49 responders to 6 weeks of placebo administration who completed a randomized clinical trial (6), the 10-day responders were more mildly and more chronically ill and reported fewer illness precipitants. However, in these and other studies (7), placebo responders and nonresponders were largely alike in almost all of the characteristics that were examined.

The current study was designed to evaluate pill-taking as a determinant of placebo response. Our object was to assess the effect of taking pills on maintenance of the placebo response after the initial 10-day single-blind trial that often constitutes the preliminary phase in randomized clinical trials with antidepressants. The questions addressed are, first, whether 10-day placebo responders who continue to receive placebo medication single-blind for 6 weeks are less likely to relapse than patients whose placebo medication is discontinued. A positive finding would suggest that pill-taking itself maintains improved mood. Therefore, the improved mood is likely a true response to placebo rather than a spontaneous improvement while the patient is taking placebo. A negative finding leaves the issue unclear. A second question is whether there are baseline variables associated with relapse after the initial 10-day improvement. A positive finding would suggest that certain kinds of patients are more likely to maintain response to placebo medication.

METHOD

Patients were potential participants in randomized clinical trials of antidepressant medication in a university-affiliated outpatient research clinic. These trials are described elsewhere (8, 9). All patients met Research Diagnostic Criteria for major, intermittent, or minor depressive disorder or *DSM-III* criteria for ma-

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jor depression or dysthymia. All had reactive mood (i.e., their mood lifted transiently in response to favorable events). All had baseline Hamilton Rating Scale for Depression scores of at least 12; no upper limit was set on these scores. The patients were between ages 18 and 55, had no substantial concurrent medical problems, and provided signed informed consent for participation in the study.

After a 10-day single-blind placebo trial, the patients' clinical status was reevaluated by their study psychiatrist. Ten-day placebo responders were identified on the basis of ratings on the Clinical Global Impression improvement scale (CGI); they received scores of 1 (very much improved) or 2 (much improved). These responders were then randomly assigned to continue to take placebo medication or were told that they had been taking placebo medication and that in view of their improvement it was not necessary to take active medication at that time. This information was framed positively as a fortunate outcome. All patients were then seen biweekly by their study physician for 6 additional weeks or until relapse, if it occurred before 6 weeks. At the end of this 6-week period, placebo medication was stopped for all patients, and all were told what they had been taking.

Baseline data included demographic, illness history, and diagnostic and clinical measures and are given in table 1. At baseline, after 10 days of placebo administration, and then at weeks 2, 4, and 6 the CGI, the 21-item Hamilton depression scale, and the SCL-90 were administered. Relapse was defined as a CGI global improvement score of 3 (minimally improved) or higher (unchanged or worse) on two consecutive weeks (an extra visit was scheduled after the first such determination). The study physician made a follow-up telephone call at week 12 to assess the patient's clinical status; CGI ratings were made at that time.

RESULTS

Over the 5-year period of the study, 58 patients were rated as 10-day placebo responders; these patients constituted 10% of all patients who received single-blind medication in clinical trials during this period. Four of the 58 patients refused to participate in the study, one moved out of the area during the trial, one refused to stop taking the single-blind placebo pills, one dropped out, and one denied 2 weeks later that he had been a placebo responder in the first place. The eight patients who did not complete the study did not differ from the 50 who did complete the study with respect to demographic characteristics, illness history, baseline illness characteristics, baseline symptoms, or severity of depression.

Forty-eight (96%) of the patients were classified as mild or moderately depressed on a 3-point illness severity scale (mild, moderate, severe). In terms of illness course, 37 (82%) of 45 patients for whom information was available reported being mostly or almost always depressed since their illness began, and 28 (78%) of the 36 patients for whom information was available had received previous psychiatric treatment. Since the modal age at onset was younger than age 20, this was a chronically ill group. Currently, 36% met criteria for dysthymia, 34% met criteria for major depressive disorder, and 30% met criteria for both diagnoses, having essentially chronic major depression (see table 1). In addition, all had reactive mood and at least one associated symptom of atypical depression (overeating, oversleeping, leaden paralysis, or pathological sensitivity to rejection). Overall, this was a middle-class, comparatively well-educated, chronically depressed group of patients, most of whose adult lives have been characterized by dysphoria and relatively low-grade but persistent depressive symptoms.

Both clinician ratings and self-report ratings documented mood improvement between baseline assessment and the end of the 10-day single-blind placebo trial. The mean CGI severity scores declined from 3.8 to 1.9 (paired t=19.2, df=48, $p<0.000$), the mean Hamilton depression scale scores declined from 14.9 to 4.6 (paired t=14.4, df=49, $p<0.000$), and the global severity index of the SCL-90 as well as each of the nine separate symptom scales showed statistically significant declines in symptoms (the t values from paired t tests ranged from 3.9 to 9.3, df=38, $p<0.000$). Overall, the patients were convincingly depressed at baseline and clearly markedly improved after 10 days of single-blind placebo.

Is Pill-Taking Necessary to Maintain Improvement Among 10-Day Placebo Responders?

Of the 50 placebo responders, 27 were randomly assigned to continue and 23 were assigned to discontinue single-blind placebo medication. Relapse was defined in terms of CGI score and corroborated by Hamilton depression scale and SCL-90 scores, as shown in table 2. Half of the patients in each group relapsed within 6 weeks (14 [52%] of the 27 patients who were continuing to take placebo and 12 [52%] of the 23 patients who were no longer taking placebo). These results clearly show that pill-taking per se did not influence maintenance of the placebo response in our patients. Further, placebo response is often not enduring in such chronically ill patients.

Patients who remained well after 6 weeks were not scheduled for further clinic visits but were called at week 12 to ascertain their status. All 11 patients whose single-blind medication had been discontinued after the first 10 days remained well. Of the 13 patients who continued to take placebo for 6 weeks and then discontinued placebo, three became depressed at week 8, 2 weeks after the placebo study and scheduled clinic visits ended. The other 10 patients remained well at week 12.

TABLE 1. Demographic Characteristics, Baseline Clinical Characteristics, and Outcome of 50 Placebo-Responsive Patients Whose Placebo Was Continued or Stopped

		Placebo Continued (N=27)		Placebo Stopped (N=23)	
Demographic or Clinical Characteristic	All Patients (N=50)	Patients Who Relapsed (N=14)	Patients Who Maintained Improvement (N=13)	Patients Who Relapsed (N=12)	Patients Who Maintained Improvement (N=11)
Age					
Mean	37	34	36	39	39
SD	10	11	10	11	7
Sex					
Men					
Number	23	9	4	4	6
Percent	46	64	31	33	55
Women					
Number	27	5	9	8	5
Percent	54	35	69	69	45
Currently married					
Number	13	0	7	4	6
Percent	26	0	54	33	54
Attended some college[a]					
Number	32	10	7	8	7
Percent	78	91	78	80	64
Hamilton depression scale score					
Mean	14.9	14.4	14.4	16.0	15.0
SD	5.1	4.6	4.4	5.4	6.4
CGI severity score					
Mean	3.8	3.8	3.9	3.8	3.6
SD	0.5	0.4	0.6	0.5	0.5
SCL-90 global score					
Mean	19.4	19.0	19.4	21.0	17.0
SD	6.2	6.1	5.1	7.5	5.4
Illness history					
Overall course[b]	3.3	3.3	3.4	3.4	3.0
Younger than 20 years at illness onset[c]					
Number	35	11	11	7	6
Percent	71	85	85	58	55
Older than 30 years at illness onset[d]					
Number	3	0	2	1	0
Percent	7	0	17	11	0
Illness had precipitant					
Number	6	1	1	3	1
Percent	11	7	8	25	9
Current diagnosis					
Number with dysthymia	18	5	5	5	3
Number with major depressive disorder	17	6	3	4	4
Number with major depressive disorder and dysthymia	15	3	5	3	4

[a] Percents are based on the number of patients for whom data were available: 11 patients who relapsed and 9 who did not in the group that continued to receive placebo and 10 patients who relapsed and 11 who did not in the group whose placebo was stopped.

[b] 3=mostly depressed, 4=almost always depressed since onset.

[c] Percents are based on the number of patients for whom data were available: 13 patients who relapsed in the group that continued to receive placebo and all of the other patients.

[d] Percents are based on the number of patients for whom data were available: 13 of the patients who relapsed and 12 who did not in the group that continued to receive placebo and nine patients who relapsed and 10 who did not in the group whose placebo was stopped.

Are There Baseline Correlates of Relapse?

Table 1 shows demographic characteristics, the illness history, and the current clinical status and diagnosis for all of the patients and for patients in each study condition who relapsed or maintained their improvement. Within each study condition there were no significant differences on any variable between patients who relapsed and those who maintained their improvement. When patients who relapsed and those who maintained their improvement were combined across study conditions, the only distinguishing variable was current marital status: significantly more of the patients who maintained their improvement were

TABLE 2. Endpoint Ratings on the CGI, Hamilton Depression Scale, and SCL-90 of 50 Placebo-Responsive Patients Who Relapsed or Maintained Improvement[a]

Measure	Patients Who Relapsed (N=26)	Patients Who Maintained Improvement (N=24)	Significance		
			t	df	p
CGI improvement rating			14.1	48	0.000
Mean	3.6	1.7			
SD	0.5	0.5			
Hamilton depression scale			5.3	42	0.000
Mean	11.8	4.4			
SD	4.0	5.2			
SCL-90 depression scale			4.1	29	0.000
Mean	2.7	1.7			
SD	0.8	0.6			

[a] For patients who relapsed, the endpoint was the second consecutive week of loss of improvement; for the patients who maintained their improvement, it was week 6.

currently married (two-tailed p=0.0005, Fisher exact test). No differences were found on any of the SCL-90 factor scores at baseline or on the variable of family history of psychiatric disorder (not shown in table 1).

DISCUSSION

The potency of placebo medication has been reported for conditions as diverse as cancer, diabetes, and the common cold. Pill-giving itself has been believed to play a specific role in this response, although we are unaware of attempts to demonstrate this. It is also unclear what elements maintain such improvement once achieved. Our findings suggest that, at least in our study group of patients with mild, mood-reactive, chronic depression, maintenance of placebo response does not require continued pill-taking or continued ignorance about the nature of the pill administered during the time when improvement occurred.

Analysis of demographic variables indicates that currently married patients may be more likely than others to maintain response to placebo medication. Given the number of comparisons made, this finding must be considered tentative and requires replication. It is possible, however, in view of our patients' sensitivity to rejection and mood reactivity, that spouses may be relieved that the patient has sought help and shown some beneficial change. This might in turn lead to improved marital interaction and thus promote and maintain "spontaneous" remission.

The placebo response observed might be due to the phasic nature of depressive disorder and might reflect spontaneous improvement as the episode drew to a conclusion. Also, our study group could have included many patients with seasonal mood disorder whose depression ended in the spring. We have some data to address these points. Midway through the 5-year data collection period, we added ratings on phasic versus chronic course of illness and on seasonality of depression. Of the 23 10-day placebo responders for whom we have such ratings, two were judged as having definite phasic illness, six as having probable phasic illness, and 15 as definitely not phasic. None was rated as having definite seasonal depression, two were rated as having probable seasonal depression, and the rest were rated as having nonseasonal depression. In view of these findings, our overall results do not appear to be due to a preponderance of patients with phasic and/or seasonal depressive disorder.

Our data directly address the role of placebo pills in maintaining placebo response. They also raise but do not resolve the question of whether pills are necessary in the initiation of placebo response in depressed patients eligible for medication trials. In view of the infrequency with which true placebo responders are identified (it took us 5 years to find 58 patients whom clinicians considered sufficiently improved and who had no ancillary symptoms such as panic attacks so that medication discontinuation was clinically acceptable), the 50% relapse rate after clinical improvement occurred, and the additional burden in terms of time and "blindness" imposed on patients, the standard procedure of an initial 10-day placebo washout should be reconsidered in designing antidepressant clinical trials. This recommendation is reinforced by the recent report of Reimherr et al. (10) that the placebo washout may have unpredictable or confounding effects; in their study, removal of "hidden" 10-day placebo responders from a 6-week double-blind trial actually diminished differences between placebo and active treatment groups.

In summary, continued pill-taking does not appear to play a substantial role in maintaining a placebo response, once achieved. With the possible exception of marital status, baseline characteristics were not useful predictors of relapse after improvement following 10 days of single-blind placebo administration. We wish to emphasize that our study group did not include severely depressed, melancholic patients or those with acute depressions, to whom our findings may not apply.

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Outcome of Patients With Chronic Affective Disorder: A Five-Year Follow-Up

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Patients with major depression, mania, or schizoaffective disorder that had been present without remission for 2 years or more at intake (N=129) were followed prospectively for 5 years, as were 580 patients who had been ill for shorter periods at intake. Despite very substantial durations of episode, three-quarters of the chronic patients recovered, although recovery occurred much later in the follow-up period than it did among the nonchronic patients. Factors associated with recovery were less severe illness at intake, lack of psychotic features, good friendship patterns in adolescence, and, most important, a relatively high maximum level of functioning in the 5 years preceding intake.

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Prognosis, among the most important judgments made by physicians, assumes even greater significance when an illness involves a wide range of possible outcomes and when persistent disability has already occurred. In the case of affective disorders, the course of illness can range from one of rapid and sustained recovery to one of unremitting symptoms with chronic, profound impairment. Moreover, chronicity, when already present, encourages hopelessness; these patients and their families are often painfully in need of assurances that recovery will eventually come.

The proportion of patients with chronic affective disorder varied widely in follow-up studies done before the widespread use of antidepressants, but one review (1) found that an average of 28% of subjects were considered unchanged on follow-up. Although the results of studies done since antidepressants became available have also been variable (2–11), a substantial portion of these studies have also found rates of chronicity above 20%. There is little consensus about predictors of chronicity. Only two baseline features—chronicity already present (6, 7) and psychotic features (6, 9)—were associated with subsequent chronicity in at least two of these more recent studies.

Only the follow-up study by Akiskal et al. (5) attempted to predict the outcome among patients who had already been ill for 2 or more years when first evaluated. Within this group, patients with "subaffective dysthymia," characterized by early onset and a prior history of good response to antidepressants, had relatively good outcomes, similar to those for patients with episodic (nonchronic) unipolar depression and substantially better than those for other chronic patients. Apparently, prior response to antidepressants was the operative variable, since patients with character spectrum disorder, marked by early onset and a poor prior response to antidepressants, were the most likely of the chronic groups to experience poor outcomes. Unfortunately, follow-up here was not systematic, and continued surveillance depended on continued clinic attendance. Moreover, the predictor variables tested were largely limited to diagnostic categories, some of which have not been widely used elsewhere.

The National Institute of Mental Health Collaborative Program on the Psychobiology of Depression—Clinical Studies has now completed a 5-year, prospective, semiannual follow-up of a large cohort of patients. Many of these patients were already chronically ill at the baseline evaluation. The extent of this evaluation and the high intensity of the surveillance during follow-up provided an unusual opportunity to address the following questions. What clinical features set chronically ill patients apart from patients who have been ill for lesser periods? Are chronically ill patients less likely to recover within a 5-year follow-up period, and do those who recover take longer to do so? Finally, what clinical features characterize the chronic patients who fail to recover?

METHOD

Earlier reports have detailed our recruitment methods and selection criteria (11, 12). Briefly, patients presenting to inpatient and outpatient facilities at five different centers (Harvard University in Boston, Rush-Presbyterian-St. Luke's Medical Center in Chicago, University of Iowa College of Medicine in Iowa City, Columbia University in New York, and Washington

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University School of Medicine in St. Louis) were invited to participate if they met the Research Diagnostic Criteria (RDC) (13) for major depressive disorder, mania, or schizoaffective disorder, depressed or manic type. The patients selected were white and were 17 years of age or older, spoke English as their primary language, had IQs of at least 70, had no evidence of organic mental disorder or any obvious terminal medical disease, lived in the area (were not transients), had knowledge of both of their biological parents, and provided written consent for participation. Selection procedures were designed to fill certain diagnostic cells with all eligible patients approached.

When they entered the study, all patients who had been in an episode of schizoaffective disorder, major depression, or mania without remission for at least 2 years were considered to have a chronic affective disorder. Many subjects had not exhibited a full syndrome of major depression or mania throughout those episodes. However, when dating onset, raters made efforts to distinguish a prodrome of a major affective disorder from a chronic intermittent depression preceding an episode of major depression. Thus, if intermittent dysphoria or a chronic minor depression preceded the onset of a full major depressive syndrome by 2 or more years, onset was dated from the beginning of the full major depressive syndrome. Moreover, if a lengthy period of intermittent dysphoria intervened between two periods of major depression, duration included only the more recent period of major depression.

For the analyses we combined patients with major depression or mania with their schizoaffective counterparts. We have noted elsewhere the considerable data showing that RDC schizoaffective disorder identifies a mixed group composed mainly of patients with affective disorder (14). For simplicity, we also combined patients who were manic at intake with those who were depressed. We sought to determine whether these diagnostic distinctions interacted with other baseline features to predict outcome among chronically ill patients.

The raters included psychiatrists, doctoral-level psychologists, and other individuals with at least bachelor's-level training in related fields. All completed a standard 2-month training period and subsequently participated in periodic training sessions involving raters from all centers. All diagnoses and clinical ratings were monitored against clinical narratives by senior raters locally and again by "expert" raters at the New York and Boston centers. This ensured fidelity across the participating centers to established rating conventions and to diagnostic criteria. Rating consistency was formally measured in several studies that have been described elsewhere (15–18).

During the index admission or within several outpatient visits, raters completed an intake battery that included the Schedule for Affective Disorders and Schizophrenia (SADS) (19). Raters also reviewed all available medical records and interviewed informants when necessary; individual SADS and RDC ratings reflected information from all these sources. Although diagnoses were revised at discharge on the basis of any newly available information, the present report uses only the diagnoses established at the initial evaluation. This database, therefore, resembles that which is available to a clinician as he or she completes a particularly thorough initial evaluation.

Each subject also provided information describing all of his or her first-degree relatives according to the Family History Research Diagnostic Criteria (FH-RDC) format (20). A subset of probands (N=614, 64%) entered a family study (12) in which all living first-degree relatives over the age of 17 were interviewed directly with a SADS—Lifetime Version format. In the present study we used a consensus diagnosis for relatives, which reflects results of the FH-RDC and of the direct SADS-L interview when these were available.

Probands participated in subsequent follow-up interviews conducted at 6-month intervals. Raters used the Longitudinal Interval Follow-up Evaluation (LIFE) (21) and, after the second year, the LIFE-II (available on request from the first author). They referred to both patient responses and medical records to quantify symptom levels, treatment, and psychosocial adjustment during the follow-up interval. Both instruments tracked psychopathology by syndrome, with special attention to the timing of recovery and relapse. According to the LIFE and LIFE-II formats, "recovery" required 8 consecutive weeks during which no more than two criterion symptoms were present to no more than a mild degree. "Relapse," then, implied preexisting recovery and occurred only when patients again met the full criteria for the corresponding disorder.

We realized that this definition is arbitrary and that the word "recovery" may carry the unwarranted implication that the subsequent course has been symptom free. On the contrary, many patients recover but then relapse and become chronically ill (7). Many clinicians think of recovery as a more sustained symptom-free state and, accordingly, in the analyses we also used alternative definitions of recovery. One definition simply extends the required symptom-free period to any 6 months, while the third, most stringent definition requires that the final 6 months be symptom free.

Treatment decisions were made by patients and their therapists and were in no way generated by the study protocol. Treatment was thus entirely naturalistic but was nevertheless carefully monitored. To facilitate analyses, the investigators developed 5-point summary scales to quantify the intensity of treatment appropriate for depression, for mania, and for psychotic affective disorder. In the analyses, any administration of a tricyclic antidepressant, a monoamine oxidase inhibitor (MAOI), lithium, ECT, or alprazolam was considered to be "at least some" antidepressant therapy. At least 300 mg/day of imipramine or the equivalent dose of another tricyclic antidepressant, 60 mg/day of phenelzine or the equivalent dose of another MAOI, or

TABLE 1. Baseline Characteristics and Recovery Among 129 Patients With Chronic Affective Disorder Followed for 5 Years—Continuous Measures

	Recovered During Any 8-Week Period				Recovered During Final 6-Month Period			
	Yes (N=100)		No (N=29)		Yes (N=49)		No (N=80)	
Variable	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age at intake (years)	38.9	14.5	37.5	13.9	41.7[a]	15.4	36.7[a]	13.4
Age at first episode (years)	24.9	14.2	26.6	12.4	29.7	13.9	24.1	11.6
Age at first outpatient treatment (years)	24.3	15.3	27.3	12.9	30.8	15.0	24.5	12.2
Duration of episode at intake (weeks)	292.5[b]	219.4	443.2[b]	255.8	303.6	253.2	340.4	244.8
Global Assessment Scale score at intake	41.3[c]	12.3	34.6[c]	9.0	42.4[d]	12.3	38.3[d]	11.5
Rating of adolescent friendship pattern[e]	3.0[f]	1.0	3.6[f]	1.2	3.0	1.2	3.2	1.1
Rating of healthiest overall functioning in 5 years before intake[g]	2.9[h]	1.0	4.2[h]	1.3	2.9[i]	1.1	3.4[i]	1.2
Rating of best level of social relations in 5 years before intake[j]	2.9[k]	1.0	4.1[k]	1.0	3.0[l]	1.1	3.4[l]	1.2

[a] t=−1.9, df=127, p=0.06.
[b] t=3.1, df=127, p=0.002.
[c] t=3.2, df=61, p=0.002.
[d] t=−1.9, df=126, p=0.05.
[e] Scale of 1–6; 6=grossly inadequate.
[f] t=2.7, df=126, p=0.007.
[g] Scale of 1–6; 6=major impairment.
[h] t=4.7, df=36, p=0.0001.
[i] t=2.2, df=125, p=0.03.
[j] Scale of 1–7; 7=grossly inadequate.
[k] t=5.0, df=127, p=0.0001.
[l] t=2.1, df=127, p=0.04.

two ECTs in a week were considered to be "vigorous" antidepressant therapy.

The univariate analyses included the baseline variables that, from our review of the literature, were potentially predictive of outcome in this sample. If categorical comparisons involved expected values less than 5, we used Fisher's exact test; otherwise we used chi-square tests with Yates' correction.

Two-tailed statistical tests were used throughout. However, since directional hypotheses were available for most of these variables, the p values for statistical significance were not adjusted for chance findings. We used, instead, logistic regression analysis to identify the baseline variables that remained predictive after statistical control for other apparent predictors.

Kaplan-Maier life table methods (22) were used to determine times to recovery and relapse. Generalized Wilcoxon tests were then used for the four group comparisons. Since these techniques described all subjects up to the point at which they left the study, the effects of censored data were minimized, and group sizes reflected all subjects who began the study. This accounts for a disparity in cell sizes between the life table analyses and the analyses that specified completion of follow-up. Since the mean times to recovery and relapse from these life tables incorporated information on dropouts, they did not generate standard deviations.

RESULTS

Chronic and Nonchronic Affective Disorder

Of 942 patients who entered the study with major depression, mania, or schizoaffective disorder, 166 (17.6%) had episodes at intake that had exceeded 2 years. When compared to the remaining, nonchronic patients by the retrospective variables listed in tables 1 and 2, chronic patients had, of course, been ill for a significantly longer period; mean values for chronic and nonchronic patients were 6 years (mean±SD=314.1±235.1 weeks) and 7 months (31.1±24.2 weeks), respectively (t=15.5, df=165, p=0.0001). These two groups were not evenly distributed across study centers—chronic patients were underrepresented at the Iowa center, where only 23 (9.4%) of 244 patients were chronic, compared to 143 (20.5%) of 698 in the remaining centers (χ^2=15.2, df=1, p=0.0001).

The 166 chronic patients were significantly less likely to be manic at intake than were the 776 nonchronic patients (N=17, or 10.2%, and N=134, or 17.3%, respectively; χ^2=5.0, df=1, p=0.03), but the chronic patients were significantly more likely than the nonchronic patients at intake to have delusions or hallucinations (N=56, or 33.7%, and N=156, or 20.1%, respectively; χ^2=14.6, df=1, p<0.0001), a diagnosis of schizoaffective disorder (N=23, or 13.9%, and N=43, or 5.5%, respectively; χ^2=14.5, df=1, p<0.0001), or cycling between mania and depression within the index episode (N=43, or 25.9%, and N=89, or 11.5%, respectively; χ^2=23.6, df=1, p<0.0001). Finally, the chronic patients had been significantly more symptomatic during their healthiest period in the preceding 5 years (t=9.4, df=209, p=0.0001).

On follow-up, the patients with chronic affective disorder experienced much longer times to recovery than did their nonchronic counterparts (figure 1). The likelihood of recovery was greatest in the first year of follow-up for both chronic and nonchronic patients, but the proportion who recovered increased much more gradually among the chronic patients. Consequently, group differences in outcome were larger at 1 year, when 76.4% (N=535) of 700 nonchronic patients and 46.6% (N=69) of 148 chronic patients had

TABLE 2. Baseline Characteristics and Recovery Among 129 Patients With Chronic Affective Disorder Followed for 5 Years—Categorical Measures

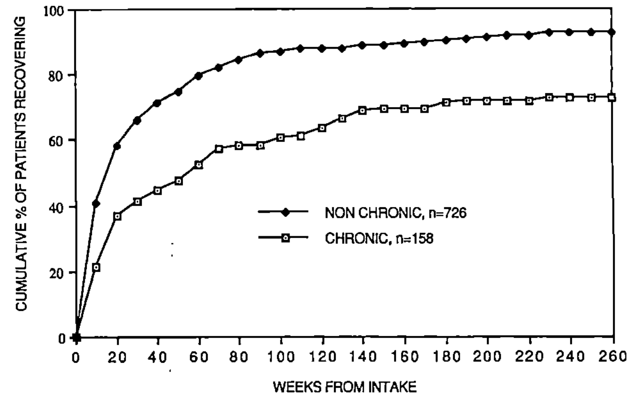
		Patients Who Recovered			
		During Any 8-Week Period (N=100)		During Final 6-Month Period (N=49)	
Variable	N	N	%	N	%
Sex					
Female	72	56	77.8	26	36.1
Male	57	44	77.2	23	40.4
Marital status					
Married	53	45	85.0	25	47.2
Never married	47	34	72.3	12	25.5
Widowed	4	3	75.0	2	50.0
Divorced or separated	25	18	72.0	10	40.0
Type of disorder					
Bipolar	29	20	69.0	7	24.1
Nonbipolar	100	80	80.0	42	42.0
Mood at intake					
Manic	11	6	54.6	1	9.1[a]
Depressed	118	94	79.7	48	40.7[a]
Cycling during index episode					
Present	33	25	75.7	10	30.3
Absent	96	75	78.1	39	40.6
Prior history of nonaffective disorder					
Present	47	35	74.5	14	29.8
Absent	82	65	79.3	35	42.7
Schizoaffective disorder at intake					
Present	18	8	44.4[b]	3	16.7
Absent	111	92	82.9[b]	46	41.4
Any psychosis at intake					
Present	47	30	63.8[c]	14	29.8
Absent	82	70	85.4[c]	35	42.7
Schizotypal features					
Present	14	9	64.3	4	28.6
Absent	115	91	79.1	45	39.1
Hallucinations					
Present	24	16	66.7	6	25.0
Absent	105	89	84.8	43	41.0
Family history of schizophrenia					
Present	0	—	—	—	—
Absent	129	105	81.4	49	38.0
Family history of depression					
Present	42	37	88.1	13	31.0
Absent	87	68	76.2	36	41.4
Family history of mania					
Present	2	2	100.0	1	50.0
Absent	127	103	81.1	48	37.8
Family history of alcoholism					
Present	20	15	75.0	7	35.0
Absent	109	90	82.6	42	38.5

[a] $p=0.05$, Fisher's exact test.

[b] $p=0.001$, Fisher's exact test.

[c] $\chi^2=6.8$, df=1, $p=0.009$.

FIGURE 1. Recovery From Index Episodes of Patients With Chronic or Nonchronic Major Depressive Disorder or Mania[a]



[a] Significant difference between groups (Wilcoxon $\chi^2=43.8$, df=1, $p=0.0001$).

recovered, than they were at 5 years when the proportions who had recovered were 93.3% (N=541) of 580 and 77.0% (N=97) of 126, respectively. Viewed in another way, three-fourths of the nonchronic patients had recovered by 50 weeks of follow-up, while 190 weeks, or nearly 4 years, had passed before three-fourths of the chronic patients had recovered. Thus, chronic patients who did recover took much longer than nonchronic patients to do so.

Predictors of Recovery From Chronic Affective Disorder

Among all patients who had been labeled chronic at intake and who completed follow-up, those who recovered for at least 2 months had had shorter episodes at intake (table 1), had been less ill according to global ratings, had been substantially less impaired when they were at their best in the 5 years preceding intake, and had had better friendship patterns in adolescence. Psychotic features and a schizoaffective diagnosis at intake were also powerful predictors of an unremitting course (table 2). The proportions of patients who recovered did not vary significantly by center; rates within centers ranged from 72.2% to 87.0% for any 2-month recovery and between 22.7% and 46.7% for the most narrowly defined recovery.

These same baseline variables, and only these variables, significantly predicted recovery when it was defined as at least 6 consecutive symptom-free months. However, when the definition was most stringent and required that the symptoms be absent or only minimal during the final 6 months, duration of the intake episode, the presence of psychotic features, and friendship patterns during adolescence ceased to be significant predictors. The remaining variables that had strongly predicted 8-week and 6-month recovery periods occurring at any time were only weakly associated with recovery status during the final 6 months. Only one variable significantly predicted recovery during the final 6 months but did not predict recovery during any 8-week period; chronic patients who were manic at intake were particularly unlikely to be in a sustained recovery at the end of follow-up.

The baseline measures that were significantly associated with 8 or more weeks of recovery (tables 1 and 2) were entered as independent variables into a stepwise logistic regression analysis. Healthiest overall functioning during the 5 years preceding intake (SADS item 1245) entered the model first ($\chi^2=19.0$, $r=-0.36$, $p<0.0001$). None of the other variables accounted for significant additional variance, although best level of social relations during the 5 years preceding intake (SADS item 1242) approached this threshold ($\chi^2=3.1$, $r=-0.09$, $p=0.08$).

In contrast, neither of these items predicted 8-week recovery among patients who were not considered chronic at intake. The 541 nonchronic patients who recovered had had ratings for healthiest overall functioning in the 5 years preceding intake that were almost identical to those of the 39 who did not recover (mean±SD=2.3±0.9 and 2.2±0.9, respectively). Ratings for the best level of social relations preceding intake were also almost identical (2.9±1.0 and 2.8±1.1, respectively).

We extended analyses of one variable, healthiest overall level of functioning that was characteristic of the subject for at least a few months during the last 5 years, since this accounted for so much of the variance in outcome. The first two levels of this 6-point scale specify 1) "absent or minimal symptoms" and 2) "no more than slight impairment in functioning; varying degrees of everyday worries and problems that sometimes get out of hand." The third level specifies "some mild symptoms" or "some difficulty in several areas of functioning, but generally functioning pretty well; has some meaningful interpersonal relationships and most untrained people would not consider him 'sick'." Recovery rates for patients with each of these first three ratings were almost identical; of 79 with ratings of 1, 2, or 3, 72 (91.1%) recovered. Recovery rates dropped substantially for the fourth level, "moderate symptoms or generally functioning with some difficulty"; 22 (71.0%) of 31 patients with this rating recovered. Decrements in recovery rates continued and were more marked for levels 5 and 6. The fifth level specified "any serious symptoms or impairment in functioning that most clinicians would think obviously require treatment or attention," and level 6 described "major impairment in several areas such as work, family relations, judgment, thinking, or mood" or "some impairment in reality testing or communication." Recovery occurred in only four (36.4%) of 11 patients with a rating of 5 and in only one (16.7%) of six patients with a rating of 6.

Treatment

Intensity of treatment at the beginning of follow-up did not predict clinical state at the end of follow-up. As we have noted, of the patients who were chronically ill when they entered the study and who completed the study, 49 were free of symptoms of major affective disorder throughout the final 6 months. Almost all of these patients (N=46, or 93.9%) and almost all of the 80 nonrecovered patients (N=73, or 91.3%) had received 4 consecutive weeks of at least some antidepressant treatment during the first 2 years of follow-up. Also during this period, 31 (63.3%) of the 49 recovered patients and 55 (68.8%) of the 80 nonrecovered patients had received a vigorous level of treatment for at least 4 consecutive weeks. The highest level of treatment received for 4 consecutive weeks was identical in these two groups; the mean±SD was 2.8±1.2 for those who would have a sustained recovery as well as for those who would not. The mean±SD number of weeks of any antimanic treatment during those first 2 years was 21.0±34.0 for the patients who would have a final sustained recovery and 33.5±39.4 for those who would not (a nonsignificant difference).

Treatment during the months immediately preceding recovery was not particularly aggressive. Among 73 patients with at least one 6-month recovery period, the highest mean±SD antidepressant score for any consecutive 4-week period in the 2 months immediately preceding the first such recovery was 1.7±1.4. The average study week at which this first 6-month recovery occurred was week 70; analysis that focused on weeks 62 through 70 for patients with no 6-month recovery revealed an almost identical highest mean antidepressant score, 1.7±1.5. Twenty-three (31.5%) of these recovered patients received at least 4 weeks of vigorous antidepressant therapy during the 2 months preceding recovery, while an almost identical proportion (N=11, or 28.9%) of the 38 nonrecovered patients had equivalent amounts of treatment between weeks 62 and 70. Corresponding numbers for patients who received any ECT during these periods were 19 of 384, or 5.0%, for those who did recover within 2 months and three of 79, or 3.8%, for those who did not.

DISCUSSION

Despite 2 or more years of unremitting major affective disorder before intake, three-quarters of these patients recovered for at least 8 weeks. Viewed in another way, however, nearly one-quarter never experienced 2 or more symptom-free months despite a follow-up of 5 years, and the chronic patients who did recover did so substantially later in follow-up than did the nonchronic patients. Thus, chronicity predicted chronicity, even among patients who eventually recovered. Clinicians should, therefore, advise both optimism and patience. Optimism must be dampened when recovery has not occurred within 1 year of prospective observation, and recovery in the coming several years is particularly unlikely for those who have remained ill during 2 years of follow-up.

The prediction of such an outcome has obvious importance. Although univariate analyses revealed a number of significant predictors, many of these were highly intercorrelated; a single variable—the healthiest overall level of functioning during the 5 years preceding intake—accounted for almost all of the explained variance in outcome. This item may have reflected the duration of serious impairment more meaningfully than did duration of episode per se. As mentioned before, the latter measure is arbitrarily delimited by the occurrence of any symptom-free period of 8 weeks or more. Consequently, an episode might be considered short despite many years of illness if only a single brief but recent symptom-free period has occurred. On the other hand, if the best period from a lengthy time span was marked by impairment, illness has probably been truly sustained.

Patients who ended follow-up with a sustained recovery were apparently not treated more vigorously at the outset, nor did relatively aggressive treatment precede the first sustained (6-month) recovery. The absence of associations between intensity of treatment and outcome may reflect several factors. First, the methods used here to summarize intensity of treatment may have been too general and may have obscured relationships between the vigorous application of particular treatments and recovery from chronic conditions. Second, chronic conditions may be more treatment resistant, in large part through selection; many patients may in fact be chronic because they have been treatment resistant before their index assessment. For such patients, the natural processes leading to recovery may have relatively greater importance than they do for patients who are less chronically ill and therefore less likely to be inherently resistant to treatment.

Baseline measures only weakly predicted sustained recovery at the end of follow-up but were more predictive of a 6-month symptom-free period occurring at some point in follow-up. Clinical measures may predict the near future more robustly than they predict more distant outcomes. Important intervening developments are more likely to accumulate with the passage of time. Previously unipolar or nonpsychotic patients may, for instance, become manic or delusional during follow-up.

Finally, the conclusion that recovery from these conditions is very likely must be tempered by the finding that it is much less so if defined more strictly. Only slightly more than one-third of the chronic patients were in a sustained (at least 6 months) recovery at the end of follow-up. Indeed, two-fifths of the patients who entered the study with a nonchronic condition were symptomatic during the final 6 months. Thus, although symptom-free periods are quite likely in the course of major affective disorder, even in previously chronic conditions, truly sustained remissions are much less frequent, at least within a 5-year period. The associated impairment is persistent and substantial, and, given the overall prevalence of the major affective disorders in the United States (23), these illnesses clearly constitute a major public health problem. Even so, sustained recovery may become more likely with the further passage of time. This is one of the possibilities that press us to extend this follow-up beyond 5 years.

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Late Luteal Phase Dysphoric Disorder in Young Women

Ana D. Rivera-Tovar, Ph.D., and Ellen Frank, Ph.D.

The authors determined the prevalence of late luteal phase dysphoric disorder in 217 university women aged 17–29 years. Unaware of the focus on premenstrual syndrome (PMS), the participants rated DSM-III-R *symptoms of late luteal phase dysphoric disorder over 90 days. Using a 30% or greater premenstrual change as an index of luteal variation, the authors found that 10 women (4.6%) met the symptom criteria during two menstrual cycles. Compared to 25 young women seeking treatment for PMS who met the same diagnostic criteria, the 10 women from the university sample reported significantly less fatigue and impaired concentration and somewhat less severe depression and overall symptoms.*

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Establishing the prevalence of premenstrual syndrome (PMS) on the basis of existing data is difficult because of the 1) lack of agreement on the syndrome's definition, 2) failure to differentiate premenstrual symptoms from a syndromal condition, and 3) past reliance on retrospective diagnoses in estimating prevalence rates. While depression and irritability are among the most common emotional manifestations of the condition (1, 2), researchers have not always focused on a similar subset of symptoms, and the lack of a common definition of PMS has led to disparate estimates of its occurrence, ranging from 20% (3) to 50% (4) of women. The recent inclusion of diagnostic criteria in the appendix to *DSM-III-R*, under the heading of Late Luteal Phase Dysphoric Disorder, has established guidelines for clinicians and researchers that can further systematic research in this area.

Prevalence rates based on retrospective data are highly questionable, since approximately 50% of women who report histories of premenstrual changes fail to confirm these reports when they complete prospective daily ratings over several months (5). Only Haskett has used prospective ratings and a rigorous application of the *DSM-III-R* criteria in a community survey (R.F. Haskett, unpublished data, 1987). He found that late luteal phase dysphoric disorder occurred in only 3.4% of women of reproductive age. This estimate is quite different from earlier figures based on retrospective self-reports and needs to be substantiated by additional prospective epidemiological data.

The average age at onset of the syndrome has also been subject to speculation, as PMS was once thought to be an affliction of women over 30. Older women did in fact predominate in many study settings, such as gynecological outpatient clinics, which led to the belief that PMS was more common in mature women (6), despite studies that found no relationship between prevalence and age (7, Haskett). As yet, however, no prospective study has specifically examined the extent or nature of late luteal phase dysphoric disorder in younger women. In our investigation we evaluated this research question in a nonclinical sample, using a design intended to overcome several of the limitations of previous studies.

METHOD

The subjects were 217 female university students fulfilling a research participation requirement for an introductory psychology course in which they were enrolled. Pregnant women, women taking oral contraceptives or any medication on a daily basis, and those with chronic health problems were excluded. The women ranged in age from 17 to 29 years (mean ±SD=18.5±1.8), were predominantly Caucasian (94%, N=205), and were regularly menstruating (cycles=21–35 days). Although an initial sample of 335 participated in symptom monitoring, the 84 women who supplied data on only one menstrual cycle and the 34 whose cycles were irregular (<21 or >35 days) were not included in the final sample. Those women did not differ from the final sample on any demographic variable.

The subjects were informed that the study was investigating the occurrence of emotional and physical changes in relation to life events in young women. Our interest in premenstrual symptoms was not disclosed at recruitment in order to 1) prevent biasing the sample toward women who believed they suffered menstrually

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related problems and 2) reduce the possible tendency to respond according to stereotypic beliefs about the deleterious effects of menstruation on mood and performance (8). Eligible participants were asked to rate the occurrence of 33 physical and emotional symptoms (including *DSM-III-R* symptoms of late luteal phase dysphoric disorder) daily over 90 days using a 6-point rating scale, ranging from 1 (no symptom or change) to 6 (extreme change). The 90-day rating period was used to ensure the collection of data on at least two menstrual cycles. The self-report instrument (Daily Assessment Form) also asked the participants to indicate any significant life events, the use of alcohol or medication, and whether or not they were menstruating.

The diagnosis of late luteal phase dysphoric disorder was determined by applying a rigorous percent-change criterion. Scores on the items on the Daily Assessment Form that corresponded to each of the 10 symptoms of the *DSM-III-R* criteria were summed and averaged over the 7 days before menses (premenstrual week) and the 7 days after the cessation of menses (postmenstrual week). For each symptom, the difference between the premenstrual average and the postmenstrual average (premenstrual minus postmenstrual) was divided by the postmenstrual average and expressed as percent change. A subject met the diagnostic criteria for a given cycle if the averages for at least five of the 10 symptom areas showed a 30% or greater premenstrual increase in severity and if all postmenstrual averages were less than 3. In an attempt to exclude cases of chronic symptoms that were heightened premenstrually (premenstrual magnification), symptoms with a postmenstrual average score higher than or equal to 3 (signifying "mild" distress) were excluded. A positive diagnosis also required that at least one of the five symptoms be one of the first four symptoms listed in the *DSM-III-R* criteria (mood lability, irritability, anxiety, or depressed mood) and that the subject meet the criteria during at least two menstrual cycles.

To determine the differences between women who do and do not seek treatment for PMS, we compared the symptoms of the undergraduates who met our syndrome criteria with those of a clinic sample of 25 women under age 30 with prospectively confirmed late luteal phase dysphoric disorder. Although similar in age range, the clinic women were significantly older than the undergraduate sample (mean±SD=25.4±3.2 versus 18.5±1.8; z=2.74, p=0.006, Mann-Whitney U test). The diagnoses for the clinic sample were derived with the same rating instrument and symptom criteria as those just outlined. Mann-Whitney U tests were used to compare the distributions and evaluate whether the treatment seekers' symptoms were more severe than those of the undergraduate sample.

RESULTS

In our sample of 217 female undergraduates, 10 women (4.6%) met all the criteria for the diagnosis of late luteal phase dysphoric disorder. The mean age of these 10 women was 20.3±4.5 years. Nine reported mild premenstrual symptoms, and only one woman's symptoms fell in the moderate-to-severe category (average premenstrual total of 4 on a 6-point scale).

TABLE 1. Symptom Severity in Young Women With Late Luteal Phase Dysphoric Disorder Who Did or Did Not Seek Treatment

	Score on Daily Assessment Form[a]					
	Treatment Seekers (N=25)		University Sample (N=10)		Mann-Whitney U Test	
Premenstrual Symptom	Mean	SD	Mean	SD	z	p
Physical discomfort	2.52	0.9	2.17	0.7	—	—
Depression	2.76	1.1	2.15	0.7	−1.55	0.06
Social withdrawal	2.00	1.0	1.98	0.8	—	—
Irritability	3.13	1.2	2.65	1.0	—	—
Fatigue	3.10	1.2	2.35	0.7	−1.75	0.04
Mood swings	3.15	1.3	2.82	1.0	—	—
Anxiety	2.89	1.2	2.62	0.9	—	—
Concentration difficulties	3.00	1.2	2.15	0.7	−1.83	0.03
Increased appetite	2.78	1.4	2.33	0.9	—	—
Decreased sleep	2.07	1.3	2.33	1.2	—	—
Increased sleep	2.50	1.2	1.94	1.0	−1.28	0.10
Total	2.58	0.7	2.22	0.6	−1.38	0.08

[a] 1=no symptom or change, 6=extreme change.

The premenstrual symptom severity ratings for the undergraduates and clinic sample are displayed in table 1. The young college women reported significantly less fatigue and concentration difficulties than the clinic women. In addition, there were nearly significant differences in depression, increased sleep, and overall premenstrual symptoms.

DISCUSSION

Our results indicate that late luteal phase dysphoric disorder, when strictly and carefully defined, is relatively rare; it was found in only 4.6% of the young college women we studied. This modest estimate is consistent with the 3.4% found by Haskett in a prospective epidemiological study of premenstrual changes among women of reproductive age in a community sample. This finding underscores the importance of using specific criteria to differentiate between premenstrual symptoms and the less common premenstrual syndrome. While isolated or minor premenstrual changes are reported by at least 75% of women (9–12), such cases do not signal the presence of a syndromal condition that may disrupt daily activities. Although college women may not be completely representative of the population of late adolescent and young adult women, our large sample, prospective ratings, rigorous diagnostic criteria, and blinding of subjects to our focus on the menstrual cycle reduced the bias inherent in earlier studies. The present findings, therefore, contradict previous indications that late luteal phase dysphoric disorder is primarily an affliction of women over 30 and suggest that when strict criteria are used, the rate of PMS is quite low.

The finding that women seeking help for late luteal phase dysphoric disorder had more severe depression, fatigue, impaired concentration, and overall symptoms than undergraduates who met the symptom criteria may be a direct result of selection factors, since help seekers would tend to be more debilitated by symptoms. An alternative hypothesis, however, is that the severity of symptoms increases over time, thus accounting for more severe symptoms in the somewhat older clinic sample. Longitudinal studies may be able to answer questions about the natural course of this cyclical disorder and examine whether women with a milder syndrome in late adolescence and early adulthood are at risk for increased distress in the future. If this pattern were demonstrated, early identification of the syndrome and prompt initiation of effective preventive strategies would be warranted.

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A Longitudinal Study of Psychotropic Prescriptions in a Teaching Nursing Home

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This study clarifies the methodological pitfalls of using cross-sectional data to characterize episodic and continuous patterns of prescribing psychotropic medications in nursing homes. Although more than half of the residents in a teaching nursing home received a psychotropic drug during their 5 years of residence, less than one-quarter were continuously medicated. The authors conclude that although the rates of psychotropic prescriptions are an important entry point for concerns about quality and appropriateness of psychotropic administration to older nursing home residents, longitudinal studies including the prescribing pattern, indications, and efficacy are needed to determine more clinically meaningful indicators of quality care.

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Studies have focused on the high rates of psychotropic drug prescriptions among elderly nursing home residents. The rates of psychotropic medication prescriptions reported have varied from a low of 11% of patients in a municipal long-term care facility (1) to 74% in a large sample of elderly Medicaid nursing home residents (2). However, most studies concur that half or more of older adults in long-term care facilities will receive a psychotropic medication at some time (1–13). Most reports confirm the growing concern that the elderly nursing home resident is likely to receive not only one but often multiple psychotropic medications (12), often in combination with other centrally acting agents (2, 4, 7, 12).

Studies reported to date have involved both small and large samples and have surveyed many types of institutions, including proprietary, municipal, and Veterans Administration nursing homes. Two recent large-scale projects (8, 10) reported high prescription rates for psychoactive drugs (55%–65%) among the elderly in intermediate care facilities and rest homes in Massachusetts and also commented on the apparent lack of physician supervision and reevaluation of the continued need for medication. These studies provided important insights into psychotropic drug prescription practices but were limited to cross-sectional reports or a maximum surveillance of 1 year. Therefore, only a limited view of the chronicity or periodicity of psychotropic drug administration is available.

Buck (3), in a survey of Illinois Medicaid records for the elderly, assumed that after a patient received a psychotropic for 6 months the use became continuous and was not likely to change. Ray et al. (2) also reported on chronic recipients, suggesting that once placed on a regimen of psychotropic medications, nursing home residents were likely to be given these agents indefinitely. These studies raise questions as to the patterns of psychotropic treatment that can be answered only with longitudinal surveillance.

Our work attempts to delineate patterns of episodic versus continuous psychotropic drug treatment over a 5-year period in a teaching nursing home in order to better characterize and describe the exposure of elderly residents to these medications.

METHOD

The nursing home studied is a 200-bed, voluntary, nonprofit facility, one of four teaching nursing homes affiliated with a college of medicine and involved in the training of fellows in geriatric medicine and psychiatry. The facility has 120 skilled nursing beds and 80 health-related-facility beds. The mean age of the residents is 85 years, and the age range is 54–103 years.

Data were collected for all 91 patients who resided in the nursing home continuously during the study period (1983–1987). Prescribing practice information was obtained directly from the nurses' records of medications administered to each patient. The medications and doses administered to patients during a 30-day period in each year for 5 consecutive years were ab-

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TABLE 1. Psychotropic Medication and Number of Drugs Administered to 91 Elderly Nursing Home Residents From 1983 to 1987

Category and Number of Psychotropic Drugs	1983		1984		1985		1986		1987	
	N	%	N	%	N	%	N	%	N	%
Category[a]										
Any psychotropic	41	45	46	51	42	46	38	42	39	43
Antipsychotic	19	21	18	20	18	20	15	17	18	20
Antidepressant	11	12	19	21	14	15	15	17	13	14
Antianxiety	20	22	15	17	12	13	19	21	9	10
Antihistamine	20	22	15	17	10	11	14	15	12	13
No psychotropic	50	55	45	49	49	54	53	58	52	57
Number of drugs										
One	22	24	27	30	30	33	21	24	27	30
Two[b]	11	12	13	14	8	9	13	14	10	11
Three	7	8	5	6	4	4	4	4	2	2
Four	1	1	1	1	0	0	0	0	0	0

[a] The numbers for the individual drug categories total more than 91 because some patients received psychotropic medication from more than one category.

[b] One patient received chlorpromazine and trifluoperazine continuously; one received amitriptyline and imipramine for three of five periods; one received clorazepate and meprobamate for two of five periods; one received diphenhydramine and hydroxyzine for two of five periods.

stracted for analysis. The same 30-day period (each April) was used every year. Data were collected on the medication doses actually administered, not just those prescribed, so that "administer as needed" doses are accurately reflected. Drug administration data were collected for psychotropic medications in each of four classes: antipsychotics, antidepressants, antianxiety agents (including sedative-hypnotics), and antihistamines. Antihistamines were included as psychotropic medications because they are often prescribed for behavioral control and as sedatives. Information was also obtained regarding doses, patterns of treatment, and administration of more than one psychotropic drug. Continuous treatment was defined as the administration of at least one dose of any psychotropic medication during every consecutive period surveyed.

Stringent criteria were used regarding the inclusion and recording of psychiatric diagnoses for patients in the study. Only diagnoses made as a result of formal psychiatric consultation were recorded. Two psychiatrists served as consultants for the patients in the nursing home during the study period.

No attempt was made in this study to determine whether psychotropic drug therapy was necessary, appropriate, or effective. All psychotropic drugs administered to the patients in the sample were included in the data even if the rationale for prescribing them or the indications were unclear. These factors are clearly important but are beyond the scope of the present work.

RESULTS

The average age of the patients in the study was 87 years, and their age range was 55–103 years. Of the 91 patients, 79 (87%) were women and 12 (13%) were men. Sixty (66%) patients lived on skilled nursing floors of the nursing home, and 31 (34%) lived on health-related-facility floors. Forty-eight (53%) of the patients received a psychiatric consultation.

Table 1 reveals the number of patients who received treatment with a psychotropic agent by drug category during the study month of each year. Depending on the period, from 42% to 51% of patients received at least one psychotropic agent. The proportion of patients treated with single or multiple psychotropic agents is also shown in table 1. In any year, most of the patients who received a psychotropic were treated with a single psychotropic agent; varying levels of polypharmacy were noted in each year.

When examining psychotropic administration over the 5-year period, we identified distinct patterns of episodic and continuous treatment. Among the 91 residents, 42 (46%) received episodic treatment, and 22 (24%) were given a psychotropic agent during every consecutive period studied. Sixty-four (70%) of the patients were exposed to at least one psychotropic agent at some time during the 5-year study period, and 27 (30%) were never given these agents.

Thioridazine was the most commonly prescribed antipsychotic drug; the average dose given was 98 mg/day. Doxepin was the most frequently used antidepressant; the average dose was 39 mg/day. Diphenhydramine was the most frequently prescribed antihistamine; the average dose was 33 mg/day. Temazepam was the most commonly used antianxiety agent. The average doses of antianxiety agents varied from 9 mg/day of diazepam equivalents in the first year to 4 mg/day in the last year studied.

The most frequent mental disorder was dementia or delirium; these accounted for 21 (44%) of the 48 psychiatric diagnoses. The second most frequent diagnosis was major affective disorder, which accounted for 14 (29%) of the psychiatric diagnoses. Five patients (10% of the diagnoses) had a primary diagnosis of personality disorder, three (6% of the diagnoses) received a diagnosis of adjustment disorder, and another five (10% of the diagnoses) had diagnoses in other categories such as substance abuse, anxiety disorder, or schizophrenia.

CONCLUSIONS

Few studies have surveyed drug prescribing practices in nursing homes longitudinally; most have used cross-sectional methods. When the time of surveillance is extended to 5 years, differing patterns of episodic and continuous psychotropic drug exposure among the institutionalized elderly emerge. These findings challenge previous studies, which assumed that most psychotropic drug treatment in long-term care facilities is continuous (2–10). In our study, episodic administration was clearly more prevalent than continuous use among the patients treated with psychotropic agents. Although the total percentage of patients who were exposed to psychotropic agents over the 5-year period appears high (70%), an examination of the patterns of treatment reveals that only 24% of the patients received continuous administration. A cross-sectional survey by year would have misrepresented both total exposure and continuous treatment by overrepresenting an assumed pattern of constant use and underestimating the percentage of patients who received any psychotropic medication at all.

No study, to our knowledge, has reported a longitudinal pattern of psychotropic drug prescribing patterns beyond a 1-year period. Since it is estimated that between 25% and 30% of the elderly will require nursing home care at some time and that at least half of these patients will have a diagnosable mental illness (14), the need to study the administration of psychotropic medications is sizable. Moreover, the association of psychotropic medications with acute adverse events, including falls, hip fractures, and syncope, has been well described (15–18). In addition, because chronic adverse effects—notably tardive dyskinesia in the case of neuroleptics—appear to increase with continued administration (19), a measure of the chronicity of drug use over a longitudinal course is obviously important.

There is increasing concern over the quality and appropriateness of psychotropic prescribing practices in nursing facilities. However, neither the available data nor the methods of survey can be considered adequate to determine what might be a reasonable level of psychotropic administration. We propose that future studies concentrate on prospective, longitudinal assessments, combining the validation of medication indications with an appraisal of adverse reactions and efficacy. The goals of such studies would be a more scientific approach to the use of psychotropic medications and a more meaningful assurance of quality treatment.

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Pharmacologic Treatment of Noncognitive Behavioral Disturbances in Elderly Demented Patients

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Fifty-nine elderly residents of long-term care facilities who had DSM-III *diagnoses of dementia were studied in an 8-week randomized, double-blind comparison trial of haloperidol, oxazepam, and diphenhydramine to test the efficacy of these agents in the treatment of clinically significant behavioral disturbances in patients with dementia. All three agents demonstrated modest but significant efficacy as measured by clinician ratings of agitated behavior and activities of daily living. The absolute magnitude of improvement was greater for haloperidol and diphenhydramine than for oxazepam, but differences among groups did not approach statistical significance. Frequencies of acute adverse events during the trial were similar across the drug treatment groups. Although these drugs may differ in terms of long-term safety and efficacy, they appear to be equivalent for short-term management of agitated behavior in severely demented patients.*

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Behavioral agitation complicates the presentation and management of many elderly patients with primary or secondary dementia (1–3). This symptom is often reflected in the presence of increased and nonpurposeful motor activity, anxiety, motor tension, irritability, hostility, assaultiveness, uncooperativeness, and aimless wandering (1, 2, 4). These disturbances can be distressing and disruptive to the patients, their families, and other caregivers. When medical and iatrogenic reversible causes are ruled out, clinicians usually choose a psychopharmacologic regimen to decrease the behavioral agitation complex. The medications most commonly used to control behavioral agitation are neuroleptic, antianxiety, and sedative hypnotic agents (5).

Antipsychotic (neuroleptic) agents are widely prescribed to control behavioral problems in patients who reside in nursing homes (6, 7). Results of the few adequately designed studies available suggest moderate efficacy of those drugs in treating anxiety, excitement, hostility, and uncooperativeness (8–11). The therapeutic response to different antipsychotic agents is generally similar, although two studies (8, 9) found haloperidol to be modestly superior to thioridazine because of its effectiveness across a broader range of symptoms, including improvement in alertness and cognition (9).

Benzodiazepine agents, particularly those with short half-lives (e.g., oxazepam), have also been shown to be efficacious in treating behavioral agitation and associated symptoms in a variety of psychogeriatric patients, many of whom had a diagnosis consistent with dementia (12–17). In these studies, oxazepam was clearly superior to placebo on observed measures of agitation, anxiety, tension, and irritability. Further, oxazepam was noted to have fewer adverse side effects than chlordiazepoxide (13) and neuroleptics (17).

Nonbenzodiazepine sedative-hypnotics like alcohol, chloral derivatives, and barbiturates are the oldest anxiolytic agents used in psychogeriatric patients (3). These agents have largely been replaced by the diphenylmethanes with antihistaminic properties, such as diphenhydramine (3). However, these agents have not been rigorously tested in well-designed clinical trials.

Despite the widespread use of pharmacologic agents in controlling agitation in elderly patients, the efficacy of these different classes of psychotropic agents has not been compared in patients with a well-defined diagno-

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sis of dementia. Furthermore, the choice of an appropriate treatment necessitates that efficacy be carefully weighed against adverse effects. This paper reports the results of a double-blind comparison of haloperidol, oxazepam, and diphenhydramine in the treatment of elderly hospitalized patients with moderate to severe dementia who exhibited agitated behavior. The purposes of this study were 1) to compare the treatment efficacy of a neuroleptic (haloperidol), a benzodiazepine (oxazepam), and a nonbenzodiazepine sedative-hypnotic (diphenhydramine) on observed measures of agitation in elderly demented patients residing in a nursing home or extended care hospital ward and 2) to determine the comparative prevalence and nature of adverse side effects of these agents in this group of patients.

METHOD

Subjects

The study patients (35 men and 24 women) were drawn from chronic care wards at three facilities (the Jewish Home and Hospital for the Aged, New York; the VA Medical Center, Montrose, N.Y.; and the VA Medical Center, Lyons, N.J.) and were at least 55 years old. All patients met *DSM-III* criteria for dementia and exhibited increased psychomotor activity and its associated symptoms. Patients were given a Clinical Dementia Rating Scale (18) score by the research psychiatrist. Scores on this scale are 0=no dementia, 0.5=questionable dementia, and 1=mild, 2=moderate, and 3=severe dementia. Formal psychometric tests could not be administered to most of these patients because they were severely demented and unable to complete even simple tests such as the Mini Mental State Examination. Patients were considered agitated if they received a rating of at least 4 (moderate) on the tension or excitement items of the Brief Psychiatric Rating Scale (BPRS) (19) or at least 3 (moderate) on one of the following items from the 40-item version of the Alzheimer's Disease Assessment Scale (20): verbal aggressiveness, physical aggressiveness, pacing, fidgeting, and increased motor activity. These criteria were met on two successive ratings, separated by at least 1 week, and agreed on by two independent experienced clinical raters.

The diagnostic evaluation for each patient included obtaining a medical, psychiatric, and neurological history, physical examination, CBC, routine serum chemistries, thyroid function, and urinalysis. Some details of the clinical history and CT scans were not available for all patients. Of the 59 patients who entered the study, four had Korsakoff's syndrome, four had major strokes, eight had previous histories of alcoholism possibly related to their dementia, five had histories of transient ischemic attacks suggesting multi-infarct dementia, one had a history of major depression but was not currently depressed, and 37 had no neurological, psychiatric, or systemic disorder sufficient to cause dementia. All of this last group and some of the patients with a history of alcoholism or transient ischemic attacks met National Institute of Neurological and Communicative Disorders and Stroke criteria for possible Alzheimer's disease (21). Patients with a history of schizophrenia, convulsive disorder, Parkinson's disease, delirium, and decompensated or poorly compensated cardiac, pulmonary, or renal disease were excluded. Sixteen patients were at least partially restrained; these patients were distributed evenly across the drug groups. Informed consent was obtained from each patient's nearest relative or legal guardian in accordance with the procedures approved by the Human Subjects Subcommittees of the Mount Sinai School of Medicine and the Bronx VA Medical Center.

Study Medications

In the year before entry into this study, patients received the following medications for control of their agitation: neuroleptics, 32 patients; benzodiazepines, 15 patients; sedatives, seven patients; antidepressants, four patients; no medication, eight patients. None of the four patients who received antidepressants met *DSM-III* criteria for major depression, and seven patients were receiving more than one psychotropic medication. Patients receiving stable doses of cardiac or other medications without psychotropic effects continued to receive those drugs throughout the study. After screening, all psychotropic medications were discontinued and, after a 2-week, single-blind placebo washout period, all patients who continued to meet the entry criteria for behavioral agitation were randomly assigned, under double-blind conditions, to receive haloperidol (0.5 mg/capsule), oxazepam (10 mg/capsule), or diphenhydramine (25 mg/capsule). The medications were packaged in capsules identical to those administered during the single-blind placebo washout phase.

Patients began with one or two capsules/day, and for the first 2 weeks the dose was adjusted daily by a research psychiatrist who was blind to the drug so that an optimal clinical response for each patient could be determined. The maximum daily doses allowed were 5 mg for haloperidol, 60 mg for oxazepam, and 200 mg for diphenhydramine. After the first 2 weeks of dose adjustment, patients received constant doses throughout the remainder of the study, a maximum of 4 additional weeks. Patients were allowed to receive up to 1500 mg/day of chloral hydrate when needed to control agitation above and beyond that treated by the study medication. Similarly, patients were allowed to receive up to 2 mg/day of benztropine for the treatment of extrapyramidal symptoms when they appeared.

Behavioral Ratings

Behavioral ratings were performed weekly by two experienced clinical raters. Behavior ratings were made on items from three complementary scales: 1) the tension and excitement items (each scored 0–7) from the BPRS, 2) the five items already mentioned (each scored 0–5) for behavioral agitation from the Alzheimer's Disease Assessment Scale, and 3) the seven items (feeding, toileting, dressing, grooming, physical ambulation, bathing, and sleeping, each scored 0–5, plus a score of 0–5 for uncooperativeness with staff in each area) of the Physical and Self Maintenance Scale for activities of daily living (22). Additional behavioral ratings were obtained weekly by ward nurses using the Nurses' Observation Scale for Inpatient Evaluation (NOSIE) (23). (Because of schedule changes by ward nurses it was impossible to have the same nurses evaluate patients throughout the study.) Adverse events were recorded by the treating psychiatrist using the Treatment Emergent Symptoms Scale (24).

The weekly amount of chloral hydrate administered for agitation was also recorded and was included in the analysis as an outcome measure. In all analyses of treatment effects, the baseline values were those obtained at the end of the placebo washout period.

Patient Withdrawal From Study

Of the 59 patients who entered the 8-week protocol, 52 (18 who were given haloperidol, 17 who were given oxazepam, and 17 who were given diphenhydramine) completed the entire protocol and were included in the 8-week analysis. Fifty-seven patients (20 receiving haloperidol, 19 receiving oxazepam, and 18 receiving diphenhydramine) completed at least 2 weeks of the double-blind phase of the protocol and are included in the endpoint analysis. Two patients (both receiving diphenhydramine) refused to comply with the protocol before completing 2 weeks of drug treatment and were not included in the endpoint analysis. Of the five patients who were withdrawn after 2 weeks of drug treatment but before the end of the study, three (two receiving haloperidol and one receiving oxazepam) were too sedated, one (receiving diphenhydramine) was too agitated, and one (receiving oxazepam) suffered from excessive extrapyramidal symptoms. One patient died in the last week of the study from non-drug-related causes.

Statistical Analysis

The primary test for significant change over time and for differences in treatment response among groups was the analysis of variance (ANOVA) performed on each of the behavioral rating scales and the amount of chloral hydrate medication administered. The analyses reported here include only patients who completed the entire study. An additional set of endpoint analyses were done including all patients who received more than 2 but less than 6 weeks of treatment with the study medications. Since the results of the endpoint and 8-week analyses were nearly identical, only the 8-week analyses will be presented. The prevalence of treatment-emergent symptoms was compared among groups as well.

TABLE 1. Demographic Characteristics of 59 Patients With Dementia Given Haloperidol, Oxazepam, or Diphenhydramine

	Sex		Age (years)		Clinical Dementia Rating Scale Score	
Patient Group	M	F	Mean	Range	Mean	Range
Haloperidol (N=20)	10	10	76.5	58–96	2.78	1–3
Oxazepam (N=19)	12	7	73.3	59–97	2.76	1–3
Diphenhydramine (N=20)	13	7	76.1	62–99	2.66	1–3

RESULTS

There were no significant differences among the three medication groups with regard to age (F=0.51, df=2, 57, p>0.10), sex (χ^2=1.05, df=2, p>0.10), or severity of dementia as assessed by the Clinical Dementia Rating Scale (F=0.30, df=2, 57, p>0.10) (see table 1). The mean±SD daily dose of medication after the first 2 weeks of dose adjustment was 1.5±0.9 mg of haloperidol, 30.0±19.4 mg of oxazepam, and 81.3±48.5 mg of diphenhydramine (approximately three capsules per patient).

The mean scores of patients on the relevant items from the Alzheimer's Disease Assessment Scale, the BPRS, the Physical and Self Maintenance Scale, and the NOSIE after the 2-week placebo washout period (baseline) and after 6 weeks of study medication (week 8) are listed in table 2, which also lists the percent of improvement on each measure. A 3×2 ANOVA comparing study groups at baseline and week 8 indicated that there was no significant difference among groups in the amount of change from baseline to week 8: the interaction of Time with Group was not significant. However, there was a significant reduction in Alzheimer's Disease Assessment Scale agitation scores over time in all three groups. This reduction in agitated behavior for all groups was also suggested by the significant Time effects observed when the BPRS and the Physical and Self Maintenance Scale were used as the dependent measures. However, no interaction of drug Group with Time was observed either for the BPRS or the Physical and Self Maintenance Scale, indicating that the changes from baseline to week 8 were not different in any of the three drug groups. A comparison of individual items of the Alzheimer's Disease Assessment Scale (verbal aggressiveness, physical aggressiveness, pacing, fidgeting, increased motor activity) and

TABLE 2. Clinical Rating Scale Scores of Patients With Dementia Given Haloperidol (N=18), Oxazepam (N=17), or Diphenhydramine (N=17)

Variable	Baseline		8 Weeks		Improvement %	ANOVA for Baseline Versus 8 Weeks (F)		
	Mean	SD	Mean	SD		Group by Time (df=2, 48)	Time (df=1, 48)	Group (df=2, 48)
Rating scale score								
Alzheimer's Disease Assessment Scale						0.4	20.3^a	1.2
Haloperidol	11.00	5.95	8.39	6.09	24			
Oxazepam	11.50	4.90	9.12	4.33	21			
Diphenhydramine	9.82	3.68	6.12	4.78	38			
BPRS						0.8	6.3^b	0.3
Haloperidol	6.33	3.01	4.78	2.44	24			
Oxazepam	5.81	2.17	5.50	2.71	5			
Diphenhydramine	5.67	2.72	4.47	2.85	21			
Physical and Self Maintenance Scale						0.5	10.2^a	1.9
Haloperidol	42.17	12.95	37.89	15.36	10			
Oxazepam	45.75	11.02	43.68	11.47	5			
Diphenhydramine	39.35	10.36	34.76	9.94	12			
NOSIE						<0.1	<0.1	4.6^b
Haloperidol	78.19	7.67	78.31	9.45	−0.2			
Oxazepam	80.69	9.10	80.69	9.89	0			
Diphenhydramine	73.47	5.88	73.00	11.53	0			
Treatment Emergent Symptoms Scale						1.4	<0.1	<0.1
Haloperidol	0.18	0.60	0.27	0.65	$—^c$			
Oxazepam	0.40	0.84	0.10	0.32	$—^c$			
Diphenhydramine	0.14	0.38	0.43	0.78	$—^c$			
Number of 500-mg chloral hydrate capsules per week						0.3	2.1	1.4
Haloperidol	2.38	3.57	2.00	2.89	$—^c$			
Oxazepam	1.36	1.65	0.92	1.90	$—^c$			
Diphenhydramine	1.64	2.44	0.57	1.16	$—^c$			

[a] $p<0.001$.
[b] $p<0.02$.
[c] Not meaningful because of the low base rate.

BPRS (tension, excitement) also indicated no significant differences in the level of agitation among the drug groups at endpoint.

Possibly because most participating nurses had little experience with the NOSIE, this scale was not sensitive to the treatment effects of any drug. NOSIE scores were significantly lower in the diphenhydramine group, but this was evident before as well as after treatment. Since there was no indication in any of the other measures of a difference among groups at baseline, the most plausible explanation is that this reflects a rating bias on the part of some nurses who rated some of the diphenhydramine patients.

A 3×2 ANOVA comparing amount of chloral hydrate (500 mg capsules) administered at baseline and at week 8 revealed no significant differences among groups in the amount of change over time. There was a slight but not significant decrease in the amount of chloral hydrate used in all groups over time, and there was clearly no difference among groups. Finally, an ANOVA revealed no significant differences because of Group, Time, or their interaction in the number of side effects reported on the Treatment Emergent Symptoms Scale. Since the numbers of symptoms reported on the Treatment Emergent Symptoms Scale were uniformly low, percentage changes on this measure are not particularly meaningful.

DISCUSSION

The three drugs tested in this study were about equally, if modestly, efficacious in the treatment of behavioral agitation in elderly patients with dementia. Haloperidol and diphenhydramine demonstrated slightly but not significantly greater clinical efficacy than oxazepam, as evidenced by improvements in activities of daily living as well as clinical ratings of behavioral agitation. Because an inactive placebo group was not included, it is conceivable that the modest improvements observed in the objective ratings of behavioral agitation were due to factors other than drug treatment. However, experience in previous clinical trials with neuroleptics (10, 11) and benzodiazepines (13) has demonstrated the efficacy of these agents over placebo. In addition, it was the clinical judgment of the treating physicians at the three sites that few patients could be managed for 8 weeks without regular pharmacologic treatment.

These results are consistent with the limited data previously reported in the literature (8–17, 25, 26), which suggest that psychopharmacologic treatment of noncognitive behavioral disturbances in elderly demented patients is generally associated with only modest improvements in behavioral control. However, no study has examined the effect of pharmacotherapy on activities of daily living in elderly demented patients (26). In the present study, statistically significant improvements in this clinical outcome measure were obtained. This suggests that agents from different psychotropic classes (e.g., neuroleptics and sedative-hypnotics), in low doses, may be effective in the treatment of noncognitive behavioral disturbances in severely demented patients and that the drug of choice may be selected on the basis of differences among these agents in side effects or consequences of subchronic or chronic treatment with these agents.

The conclusions of this study are clearly limited by the types of patients included in the trial. These were moderately or, in most cases, severely demented individuals whose cognitive impairment was due to one of several diseases or more than one disease. Neurochemical studies have demonstrated relatively specific loss of some neuronal populations in patients with Alzheimer's disease (27), the most common cause of dementia. The extent of cholinergic cell loss has been shown to correlate with the severity of dementia in Alzheimer patients (28) and those with other types of dementia (29). Attempts to develop pharmacologic treatments for the cognitive impairment of dementia have focused primarily on drugs that enhance cholinergic activity (30). No specific neurochemical abnormality has been implicated in the development of agitated behavior in patients with Alzheimer's disease or other kinds of dementia. Since agitation usually appears only in fairly advanced cases of Alzheimer's disease, it is likely that multiple neurotransmitter abnormalities are involved. From a clinical perspective the most important treatment goal for patients such as those included in the present trial is to control agitated behavior without worsening cognition or producing other unacceptable side effects. The present results suggest that this may be done through drugs acting on several different neurotransmitter systems.

Treatment with haloperidol, diphenhydramine, or oxazepam, however, may be associated with different potential adverse consequences in psychomotor and cognitive areas, particularly in elderly patients. Subchronic or chronic use of haloperidol may be associated with the development of tardive dyskinesia, especially in elderly patients (31). Although we found no evidence of the development of new involuntary movements in the patients treated with haloperidol in this study, a treatment period of 2–6 weeks is generally too brief to observe this adverse effect of neuroleptic treatment. Accordingly, the possibility that tardive dyskinesia may develop in such patients treated chronically with neuroleptics will require further investigation.

Unlike the long-term risk of tardive dyskinesia with neuroleptics, however, both neuroleptics (particularly those with low potency) and agents such as diphenhydramine or oxazepam may have a more rapid and readily observable adverse effect on baseline cognitive function, due, in part, to antagonism at central cholinergic receptors (32). Although this possibility has not been formally addressed in previous studies (25), it is of note that no patient was rated as developing a toxic confusional state on the Treatment Emergent Symptoms Scale or displaying more trouble remembering on the NOSIE during treatment with any of the agents used in this study. Although this is consistent with the relatively low doses administered, it is possible that the benefits of pharmacotherapy on behavioral agitation in these patients overcame possible adverse effects on clinically observable cognitive function. It is also conceivable that, since formal psychometric testing was not possible, subtle worsening of cognitive functions in some patients was missed. Accordingly, future investigations examining the effects of these medications in extended clinical trials, particularly those involving less demented and outpatient samples, should include a more formal assessment of the effects of these agents on cognitive function.

In conclusion, pharmacotherapy with neuroleptic, benzodiazepine, and sedative-hypnotic agents appears to be modestly efficacious in the treatment of noncognitive behavioral disturbances in elderly demented patients residing in long-term care facilities. Among the three agents examined, haloperidol and diphenhydramine appeared slightly superior to oxazepam in improving performance of activities of daily living. In addition, it is possible that some individuals may respond preferentially to one class of drugs over another. Further studies are needed to investigate the differential long-term efficacy of these agents in demented elderly patients living in nursing homes. In addition, future studies should extend investigation to outpatient populations of demented but less severely impaired elderly patients in order to determine the efficacy of these agents in controlling the noncognitive behavioral disturbances of affected patients and prolonging the period of functioning of these patients in the community.

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Dyskinetic Movements, Cognitive Impairment, and Negative Symptoms in Elderly Neuropsychiatric Patients

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The presence or absence of tardive dyskinesia, cognitive status, and psychopathology were assessed in a group of elderly male psychiatric patients (N=49) in a nursing home setting. Twenty-five patients were found to have tardive dyskinesia, which was associated with a greater degree of cognitive impairment and negative symptoms. This finding was not related to obvious macroscopic organic pathologies, which were less prevalent in the dyskinetic patients. In fact, patients with frontal lesions (primarily lobotomies) had a significantly lower prevalence of tardive dyskinesia.

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Higher levels of cognitive impairment and/or negative symptoms have been reported in tardive dyskinesia in some studies (1–3) but not in others (4–6). Similarities between tardive dyskinesia and levodopa-induced dyskinesia, and the reduction of the signs of tardive dyskinesia by dopamine blocking agents, suggest that the basal ganglia are involved in tardive dyskinesia (7). Moreover, a loss of substantia nigra cells and more brainstem gliosis have also been reported in tardive dyskinesia (8). Dysfunction of the basal ganglia may have a primary role in the production of cognitive impairment and negative symptoms in a broad range of neuropsychiatric disorders (9).

In an effort to establish an association between tardive dyskinesia, cognitive impairment, and negative symptoms, these variables were examined in a group of elderly psychiatric patients in a nursing home setting.

METHOD

Subjects

The subjects were 49 men housed on four nursing home units of the John L. McClellan Memorial Veterans Administration Medical Center. The subjects were examined consecutively and were selected because the primary diagnosis in their hospital chart was schizophrenia. Almost all subjects had begun treatment with antipsychotic medications between 1957 and 1960. Ten subjects had received no psychoactive medication for at least 2 months before the current study. Hence, the modal and mean duration of treatment with antipsychotic medications approximated 30 years. Frontal lobotomies had been performed on nine subjects between 1950 and 1957. Another patient had a self-inflicted gunshot wound to the head in 1953; it had damaged both frontal lobes and rendered him blind. Twenty-six subjects had received at least one course of ECT.

Procedure

Dyskinesia was assessed with the Abnormal Involuntary Movement Scale (AIMS) (10), which was administered by a trained neuropsychiatrist (C.N.K.) who was unaware of the subject's cognitive performance. Tardive dyskinesia was diagnosed according to the criteria of Schooler and Kane (11). Patients were classified as to the presence or absence of tardive dyskinesia. To meet criteria for tardive dyskinesia the patient must have scored 2 or above on at least two of the measures of facial expression or 3 or above on at least one of these facial measures. The clinical status and treatment regimens of these patients were extremely stable. Because of this, any dyskinesias detected were not likely to be of the withdrawal type. Interrater reliability of the clinical diagnosis of tardive dyskinesia was examined. Twenty-one of the 49 inpatients were independently evaluated with the AIMS by a second research neuropsychiatrist (H.S.B.) on a separate occasion.

A probable lifetime psychiatric diagnosis was established by trained psychiatric residents (A.P. or L.A.) using a structured chart review, the Diagnostic Evaluation After Death (12). This procedure was used because of the advanced age of the patients, the deteriorated mental state of some of the patients, and the frequent absence of knowledgeable relatives. With this instrument, the diagnosis of schizophrenia relies on the Feighner criteria (13), while that of schizoaffective disorder and affective disorder relies on Research Diagnostic Criteria (14). Thirty-eight subjects met the

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criteria for a probable lifetime diagnosis of schizophrenia, and another four patients met the criteria for schizoaffective disorder. One patient met the criteria for the lifetime diagnosis of major depression, another for bipolar disorder, two for alcoholism, and one for opiate addiction. One subject, who had failed to pass eighth grade and then had self-deprecatory hallucinations and delusions concerning his intelligence, in the absence of depressed mood, was diagnosed as mentally retarded with an atypical psychosis. The lifetime psychiatric diagnosis for one patient could not be determined.

In addition to the chart review diagnosis, the subjects were diagnosed according to *DSM-III-R* criteria by a psychiatrist (C.N.K.) who had not been involved in the chart review process. Thirty patients met *DSM-III-R* criteria for schizophrenia, six for residual schizophrenia, and one for schizoaffective disorder. Two subjects had no current psychiatric diagnosis. Cerebral vascular disease (N=3), chronic sepsis (N=1), and the neurological residual from the self-inflicted gunshot wound to the head complicated the interpretation of psychiatric signs and symptoms and necessitated the diagnosis of organic mental syndrome in five of the patients. The retarded subject met the criteria for atypical psychosis. One patient continued with the diagnosis of opiate abuse. One patient met the criteria for major depressive disorder and two patients for bipolar disorder.

Cognitive status was quantified with the Neurobehavioral Cognitive Status Examination (15). This valid and reliable instrument (16, 17) addresses seven categories of cognitive function: orientation, attention, language, construction, memory, calculation, and reasoning. The language score represents the sum of three subtests (comprehension, repetition, and naming) and the reasoning score the sum of two subtests (similarities and judgment). Four subjects refused to cooperate with all or part of the examination, and a visually impaired subject could not perform the naming subtest of language and the construction tests. Hence, there are varying numbers of subjects for some categories of the examination. Negative symptoms were the sum of the emotional withdrawal, blunted affect, and motor retardation items of the Brief Psychiatric Rating Scale (BPRS) (18). A score for positive symptoms was determined similarly from the relevant BPRS items, which included disorientation, disorganized speech, grandiose statements, unusual thought content, and hallucinatory statements. Reliability calibration training for the BPRS is ongoing, and there are high levels of interrater agreement (i.e., for 22 subjects rated simultaneously by two independent raters using the BPRS). Intraclass correlation coefficients (ICCs) were computed for the total BPRS score, the positive symptoms subscale, and the negative symptoms subscale (ICC=0.99, df=21, 21, for total scores; ICC=0.98, df=21, 21, for the positive symptoms subscale; ICC=0.97, df=21, 21, for the negative symptoms subscale; all comparisons significant at $p<0.05$).

Blink rate, a putative correlate of brain dopamine activity (19), was counted by direct observation, averaged over a 3-minute period while the subject was sitting quietly. The rate is expressed as blinks/minute. Blinks were not measured in one subject who had had bilateral surgery for cataracts.

Parkinsonism was rated as present or absent on the basis of the presence or absence of rigidity, cogwheeling, or characteristic tremor in the upper extremities.

Statistical Analysis

Nonparametric analyses were selected for between-group comparisons of dependent variables because of the low number of subjects in some patient subgroups (i.e., patients with psychosurgery) and because passing the screening questions on the Neurobehavioral Cognitive Status Examination yields high scores for a given cognitive function. Hence, the scores were not normally distributed. Differences in the proportion of patients with and without dyskinesia who also had other subdiagnoses, such as organic mental syndrome, parkinsonism, frontal lobe injuries, and residual schizophrenia, were analyzed with Fisher's exact test (20). Differences between the dyskinetic and nondyskinetic patients with regard to demographic variables, cognitive function scores, negative symptoms, positive symptoms, and blink rate were examined with the Mann-Whitney U test (20). With regard to cognitive function and psychopathological measures, the comparisons between the dyskinetic and nondyskinetic patients excluded the five patients with organic mental syndromes, all of whom were nondyskinetic and three of whom had among the lowest cognitive performance scores obtained. Finally, correlations between these variables were assessed with the nonparametric Spearman's statistic (20). The kappa statistic was used to assess the interrater reliability of the presence or absence of tardive dyskinesia.

RESULTS

Twenty-five patients were found to have tardive dyskinesia. There was an overall 71% agreement between the two independent raters. The interrater reliability was in the fair to good range (kappa=0.43). The mean±SD age of subjects with tardive dyskinesia was 69±6 years, the mean duration of illness was 41±8 years, and the mean educational level was 9±3 years. These values were not significantly different from those in the 24 nondyskinetic patients, whose mean age was 68±8 years, mean duration of illness was 42±6 years, and mean educational level was 11±3 years. The mean dose of medication in terms of chlorpromazine equivalents was 742±969 equivalents for the nondyskinetic patients and 359±545 equivalents for the dyskinetic patients ($p>0.20$; the means exclude one patient from each group who received fluphenazine decanoate injections). At the time of examination, five dyskinetic and five nondyskinetic patients had not received psychotropic medications for 2 months or longer. The proportion of patients with a lifetime or current diagnosis of active schizophrenia was not significantly different in the dyskinetic and nondyskinetic groups (23 of 25 patients versus 19 of 24 patients, $p \geq 0.50$, Fisher's exact test).

All six patients with residual schizophrenia had tardive dyskinesia ($p=0.02$, Fisher's exact test). In contrast, the five patients with organic mental syndromes ($p=0.02$, Fisher's exact test) and seven of nine patients with lobotomies ($p=0.07$, Fisher's exact test) were not dyskinetic. The patient with the self-inflicted frontal lobe wound was grouped with the lobotomy patients to examine long-standing frontal cortex injury, and eight of the 10 subjects with such injuries were without dyskinesia ($p=0.04$, Fisher's exact test). In addition, 11 of 15 patients with presumed neuroleptic-induced parkinsonism were not dyskinetic ($p=0.04$, Fisher's exact test).

With regard to cognitive function, patients with tardive dyskinesia had relative impairments compared with nondyskinetic patients in memory (mean scores= 3.0±2.5 versus 5.4±3.9; Mann-Whitney $U=260.5$, $p \leq 0.05$), calculating ability (2.1±1.7 versus 3.4±1.2; $U=279.5$, $p<0.05$), and reasoning (3.4±3.1 versus 5.8±4.0; $U=279.5$, $p<0.05$). No differences were found with orientation, attention, or language ($p= 0.25$–0.90).

Negative symptoms were significantly more severe in the dyskinetic patients than in the nondyskinetic patients (mean negative symptom scores=9.3±3.5 versus 6.5±3.5; $U=133.7$, $p<0.02$). Positive symptoms were not different in the two groups (11.6±9.0 versus 12.7±9.6; $p>0.55$). Slight but significant correlations were found between negative symptoms and two cognitive items, memory and calculation ($r_s=-0.32$ and -0.36, respectively, $p<0.05$).

Within the dyskinetic group, there were no significant correlations between severity of the involuntary movements, even when separated into facial and limb-truncal scores (21), and any aspect of cognitive function. In addition, there was no positive correlation between severity and negative symptom scores.

Finally, the mean blink rate of 21±20 blinks/min in subjects without involuntary movements was not significantly different from the rate of 18±14 blinks/min in patients with involuntary movements.

DISCUSSION

Tardive dyskinesia was associated with more cognitive impairment and negative symptoms in this group of elderly male psychiatric patients. The significantly lower prevalence of secondary mental syndromes and frontal lobe lesions (primarily iatrogenic) in the dyskinetic patients than in the nondyskinetic patients in the present study suggests that more cognitive deficits and negative symptoms cannot be explained by confounding macroscopic brain disease. One group has suggested that cognitive impairment, negative symptoms, and tardive dyskinesia are associated and may result directly from the schizophrenic process (22, 23). In the current study involving patients with extensive antipsychotic treatment histories, the prevalence of dyskinesia was substantially higher than that reported by Owens et al. (22) in never-medicated schizophrenic patients. The current results, then, would appear to agree with the bulk of the literature suggesting that treatment with antipsychotic medications can at least promote tardive dyskinesia in vulnerable individuals.

Insofar as tardive dyskinesia may be the result of striatal dysfunction, the dysfunction of these structures in psychosis could be secondary to a lesion elsewhere, e.g., in the frontal cortex (24, 25), but it also could be primary. Moreover, some cognitive impairments are difficult to attribute to specific brain structures. For instance, impairments caused by bilateral lesions of the head of the caudate can resemble those produced by lesions of the frontal cortex in both nonhuman primates (9) and in humans (26). If a primary dysfunction in the frontal cortex underlies the cognitive impairment and negative symptoms in patients with tardive dyskinesia, one would expect lobotomies and other obvious frontal lesions to be more prevalent in these patients. We found the opposite: that is, we found frontal lesions to be significantly less prevalent in patients with tardive dyskinesia.

Our findings may suggest a primary role for the striatum in the pathogenesis of cognitive impairment and negative symptoms in neuropsychiatric disorders of multiple types, i.e., our findings suggest that negative symptoms and cognitive impairment may be manifestations of subcortical dementia (9, 26). The association of cognitive and negative symptoms with tardive dyskinesia found in patients with affective disorder (27) also supports this hypothesis.

Like Waddington et al. (3), we found no pattern of cognitive deficits to implicate a specific cortical brain region. This, too, is consistent with the hypothesis that subcortical dysfunction may play a role in the expression of cognitive impairment and negative symptoms.

Although one post-mortem study (28) documented previous involuntary facial movements in 12 of 19 leukotomized subjects, most previous studies have generally not found a positive relationship between lobotomies and tardive dyskinesia (29). Comparisons with these earlier studies are difficult because of the advanced age and extended duration of antipsychotic medication treatment of the subjects in the present study.

The present study is limited by the small number of subjects and the inability to calculate the cumulative neuroleptic exposure of these patients. Nevertheless, in view of the increasing evidence for the role of the striatum in cognition (9, 26), the present study may suggest that the disruption in basal ganglia function which results in tardive dyskinesia also may play a role in the pathogenesis of the cognitive impairment and negative symptoms in schizophrenia.

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Remediation of Cognitive Deficits in Schizophrenia

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Studies have suggested that schizophrenia is characterized by an impairment in the dorsolateral prefrontal cortex that prevents learning of some elementary information processing tasks. To test this hypothesis, the authors administered the Wisconsin Card Sorting Test to 16 schizophrenic inpatients with standard instructions and either contingent or noncontingent reinforcement. Performance was markedly impaired under each condition. A second cohort (N=12) was tested after receiving instructions plus rehearsal and feedback. These subjects' performance was comparable to nonpatient norms and was maintained on a subsequent day. The results indicate that deficits in performance on the Wisconsin Card Sorting Test are remediable, whether or not they are due to neurological impairment.

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The existence of both structural and functional brain impairments in schizophrenia is documented by an extensive body of literature (1–4), but the precise neurological basis of the illness is still controversial. There is considerable support for both structural and biochemical hypotheses, but the evidence is far from consistent (5). One of the most compelling hypotheses about the locus of schizophrenic brain dysfunction is that the disorder involves an impairment in the dorsolateral prefrontal cortex (3). In an important series of studies, Weinberger et al. (6–8) demonstrated that, in contrast to normal control subjects, schizophrenic patients fail to exhibit increased blood flow to this area when performing a task which requires prefrontal activation. In contrast, they exhibit normal activation in other areas of the cortex while performing information processing tasks that impose different cognitive demands.

The prefrontal task employed in the Weinberger studies was the Wisconsin Card Sorting Test (9), a widely used neuropsychological task that requires subjects to categorize simple geometric forms by shape, color, or number (of objects). It is relatively easy for normal subjects but is difficult for patients with prefrontal lesions. Perhaps the most notable finding of Weinberger et al.'s series of studies was that the schizophrenic patients seemed unable to learn how to perform this task, even after coaching. Goldberg et al. (8) reported that schizophrenic subjects could perform adequately when given card-by-card feedback on the correcting sorting rule, but there was no generalization to subsequent uncoached trials. The subjects were able to learn to perform other, nonprefrontal tasks, suggesting that the deficit in performance on the Wisconsin Card Sorting Test was not due to inattention or lack of effort. Thus, Goldberg et al. concluded that failure to learn the Wisconsin card sorting task reflected a profound prefrontal dysfunction.

However, several aspects of the Goldberg et al. study raise questions about the generalizability of the results. First, the subjects were inpatients at St. Elizabeths Hospital who "had chronic unremitting illnesses, a population chosen because of the probability that they would perform poorly on the Card Sort" (8, p. 1009). It is not clear precisely what this selection method entailed, but the description implies a severely impaired sample that was somehow different from the broader population of schizophrenic patients. Second, the Wisconsin Card Sorting Test procedure imposes a set of demands that may be particularly difficult and aversive for schizophrenic patients. The procedure provides little guidance or support to patients. The initial instructions simply direct the subject to put the stimulus cards where the subject thinks they belong, and the examiner provides no feedback during the task other than saying "Right" or "Wrong" each time the subject makes a response. If the subject gets 10 trials in a row correct, the sorting rule is covertly changed by the examiner, who gives the subject no feedback other than saying "Wrong" to previously correct responses. The test is administered in sets of 64 or 128 trials. Consequently, if the subject has difficulty, he or she is presented with a long series of critical responses that offer little guidance and no encouragement. Many schizophrenic patients are highly sensitive to negative feedback, so they might find this procedure particularly distressing (10).

A third limiting factor is the training strategy employed to teach patients how to perform the task. The

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subjects in the Goldberg et al. study received three sets of 64 trials for which they received minimal or no instructions, followed by 32 trials in which they were told the correct response after each trial. This procedure temporarily increased performance accuracy above 90%, but the training paradigm had several limitations. First, the subjects had already experienced a considerable amount of failure on the initial sets of trials and were given no incentive to learn the task when training began. It cannot be assumed that severely impaired schizophrenic patients have the intellectual curiosity or inherent motivation to spontaneously invest effort on tasks like the Wisconsin Card Sorting Test. Second, it is not clear that the subjects were taught a rule for adjusting to the changing demands of the task; they may simply have been complying with the examiner's instructions, rather than actively trying to learn about the task. Third, prompting lasted for only 32 trials, in which the subjects made few errors. Thus, they had little opportunity for corrective feedback, which might have facilitated learning of a generalizable rule.

If valid, Goldberg et al.'s conclusion would have a dramatic impact on rehabilitation programs for schizophrenic patients. For example, recent efforts to enhance social functioning have emphasized training in problem-solving skills (11). This endeavor might be fruitless in the face of unremediable prefrontal impairment (12). The purpose of our study was to examine the generalizability of the Goldberg findings and determine 1) whether a less impaired sample of schizophrenic patients would exhibit marked inability to perform the task and 2) if so, whether they could learn it when provided with a positive incentive (money) for performance and with more elaborate training.

METHOD

Subjects

The subjects were 28 patients who met the *DSM-III-R* criteria for schizophrenia. All were inpatients in an acute care facility. The diagnosis was determined on the basis of a structured interview: either the Schedule for Affective Disorders and Schizophrenia (13) or the Structured Clinical Interview for DSM-III: Psychotic Disorders (14) (two different interviews were used because some subjects were initially screened for a different research protocol). Each subject provided informed consent to participate and exhibited no evidence of definite or probable organic brain syndrome or history of drug or alcohol dependence (as reported in the chart or suggested during the diagnostic interview). A patient was excluded if diagnosis, organic involvement, or substance abuse history were uncertain.

The sample consisted of 21 men and seven women; 12 were black and 16 were white. The mean age was 32.4 years (range=23–48). The subjects had a mean of 6.2 prior hospitalizations and were first hospitalized at an average age of 21.1 years. Each subject was in the midst of an acute exacerbation at the time of testing. They had been in the hospital for an average of 20.4 days before participating in this study; total hospitalization time for the current episode averaged 32.8 days. All subjects were taking neuroleptics, and the mean chlorpromazine-equivalent dose was 838.4 mg/day. The Brief Psychiatric Rating Scale was administered to all but four subjects within 1 day of testing. The results documented that the subjects were still substantially impaired: the mean±SD thought disorder summary score was 3.32±1.00, and the mean for severity of illness was 4.60±0.89 (each score based on a 7-point scale, 7=very severe impairment).

Procedure

Our initial hypothesis was that poor performance on the Wisconsin Card Sorting Test might reflect inattention and lack of effort, rather than inability to master the task. We expected that performance would be improved by providing an incentive. To test this hypothesis, we tested an initial cohort of 16 patients (cohort 1), who received either positive reinforcement (a nickel) contingent on correct responses or a noncontingent incentive (also a nickel) periodically throughout the test. Neither procedure had any effect on performance, and we consequently recruited a second cohort of 12 subjects (cohort 2) and provided contingent reinforcement supplemented with more extensive training. The procedure for each cohort comprised four phases: 1) testing under standard conditions, 2) testing with incentives and/or training, 3) testing under standard conditions, 4) testing under standard conditions on the following day.

Cohort 1. These 16 subjects were assigned sequentially to contingent reinforcement or noncontingent reinforcement. All subjects received four sets of cards. The first set (128 cards) was administered with the standard instructions described by Heaton (9) in the manual for the Wisconsin Card Sorting Test. The subjects were instructed only to place the stimulus cards where they thought they belonged. The experimenter replied "Right" or "Wrong" after each trial. If the subject got 10 successive trials correct, the experimenter changed the sorting rule without any notice.

The second set of (128) cards was also administered according to standard procedures, but the subjects were provided one of two forms of performance incentives in addition to the standard verbal feedback. The subjects receiving contingent reinforcement were told that they would be given 5 cents for each correct response. A cup was placed on the table in the subject's sight, into which the experimenter deposited a nickel immediately after a correct sort. The subjects receiving noncontingent reinforcement were told that they would periodically receive 5 cents for "trying hard." Each of these subjects was "yoked" to the preceding subject in the contingent reinforcement group and received a nickel in each trial for which the yoked partner was reinforced. Thus, a subject in the noncontingent reinforcement group received the incentive in designated trials whether or not the responses were correct but received appropriate verbal feedback, according to standard Wisconsin test procedure. A set of 64 cards was then administered under standard testing conditions (i.e., no incentives). A fourth set of (128) cards was administered under standard conditions the following day, to determine if any performance gains were maintained.

Cohort 2. The procedure for these 12 subjects was identical to that for the cohort 1 group that received contingent reinforcement except that the subjects were given the following instructions:

> Let me tell you a little about this task before we go any further. There are three ways you can match up the cards: by color, by shape, or by number. If you match by color, you would put a red card under the red pile, a yellow card under the yellow pile, etc. If you match by shape, you would put a circle under the circles, a star under the stars, and so on. Finally, if you match by number, you would put a card with one form on it under the one pile, a card with two forms on it under the two pile, and so on. Each time you choose, you should try to decide which will be correct: color, shape, or number. If you think color is correct, what would you do? Good. [*Provide correct answer with explanation if subject is incorrect or uncertain.*] How about if you think the correct choice is shape? Good. [*Prompt with correct answer if subject is incorrect.*] And how about if you think it is number? Good. [*Prompt and correct again if necessary.*]
>
> Now, I am going to pick one category to be correct: it could be color, shape, or number. That category will be correct until you get it right several times in a row. After you get several correct in a row, I will change the category that is correct. For example, if the correct category is color and you get it right for a while, I will change the correct category to shape or number. That category will be correct for a while, and then I will change it again. I can't tell you the rule in advance, but I will give you a nickel every time you get one right. If you get a nickel, that means you sorted the card correctly, and you should sort it the same way the next time. If I say "Wrong," that means you sorted with the wrong category and you should sort it a different way the next time. For example, if you match up by color and I give you a nickel, that means color is correct and you should guess it again. If you guess color and I don't give you a nickel, what does that mean? Good. [*Correct and explain if necessary.*] Then what should you do next? Good. [*Correct if necessary.*] OK, before we start, tell me what you are going to do. Good. [*Correct if necessary.*]

The experimenter then began administering the test. After each of the first five cards the subject was asked how he or she decided which pile to choose and what he or she would do with the next card. If the response indicated lack of understanding (even though the sort may have been correct), the decision rules were reviewed in the same manner as in the initial instructions. This questioning and review was repeated after cards 32–37. After this set of 128 cards was completed, an unreinforced and unprompted set of 64 cards was administered. A fourth set of (128) cards was administered the following day, as with cohort 1.

RESULTS

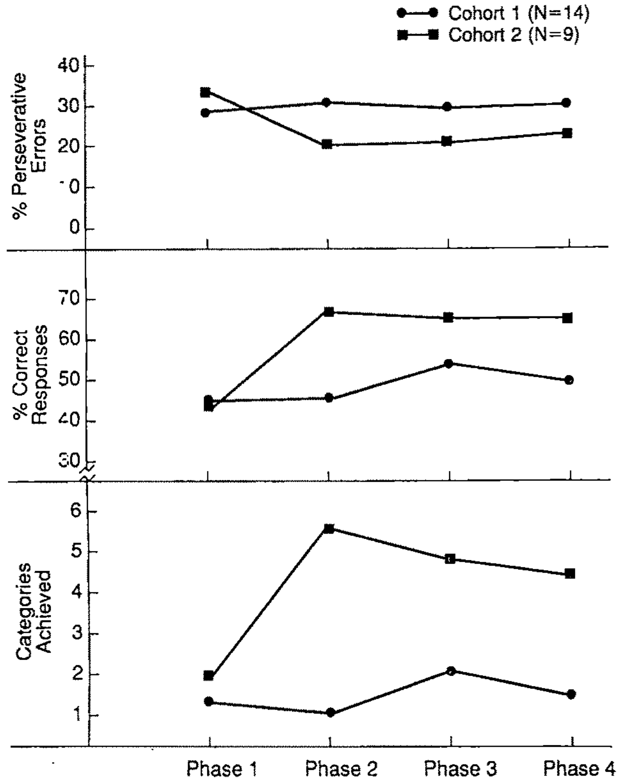
The subjects in the second cohort were recruited and tested after the tests with the first cohort had been completed. A series of t tests and chi-square analyses demonstrated that the two cohorts were equivalent on all demographic variables, medication levels, and history of treatment. Two subjects in cohort 1 and three in cohort 2 completed five categories (i.e., gave 10 correct responses in succession) on the first set of cards (before incentives or instructions were provided), which is equivalent to the performance of the "normal" subjects in Heaton's standardization sample (9). As further improvement was unlikely, these subjects were excused and did not complete sets 2–4. In the analyses reported, there were seven subjects each in the groups receiving contingent and noncontingent reinforcement and nine in the instruction group. As the subjects were not assigned to the cohorts on a random basis, the data technically violate the assumptions underlying the analysis of variance. Hence, we opted to first analyze the data from the two cohorts separately.

The two groups in cohort 1 were compared with 2×4 (Group by Phase) repeated measures analyses of variance (ANOVAs) on categories completed, correct responses, and perseverative errors. As only 64 cards were administered in phase 3, scores for this phase were prorated. None of the differences was significant. Both groups performed at or below the level of Heaton's brain-damaged samples (9), and neither exhibited any evidence of learning. Four subjects failed to complete more than one category in any of the sets, and five others completed no more than two categories in any set.

The data for cohort 2 were analyzed with a series of one-way repeated measures ANOVAs. The results (figure 1) were dramatically different. Performance was very poor on the first set of cards but improved significantly with the introduction of instructions in phase 2. The improvement was maintained in phases 3 and 4, after instructions and incentives were withdrawn.

A series of 2×4 ANOVAs (Cohort by Phase) was conducted to compare cohort 2 with the combined groups from cohort 1. Degrees of freedom were adjusted by means of the Greenhouse-Geisser procedure (15). These analyses confirmed the pattern suggested by the separate cohort analyses. As shown in table 1, two of the three analyses were characterized by significant phase effects, and all three indicated significant Cohort by Phase interactions. This pattern reflects the improvement in cohort 2. Orthogonal contrasts documented that the subjects in cohort 2 performed significantly better in phases 2, 3, and 4 than they did in

FIGURE 1. Performance on the Wisconsin Card Sorting Test of Schizophrenic Patients Given Standard Instructions and Contingent or Noncontingent Reinforcement (Cohort 1) or Contingent Reinforcement and Instructions Plus Rehearsal and Feedback (Cohort 2)[a]



[a] Phase 1=standard conditions, phase 2=incentives and/or training, phase 3=standard conditions, phase 4=standard conditions on the following day.

phase 1 ($p<0.02$ for each dependent variable). In addition, the slight performance declines across phases 3 and 4 were not significant.

DISCUSSION

The results for cohort 1 are consistent with the Goldberg et al. (8) findings. Our subjects exhibited marked deficits in performance on the Wisconsin Card Sorting Test, having as much or more difficulty than patients with frontal brain damage. Adding contingent or noncontingent incentives had no effect on performance, suggesting that the poor performance was not a simple result of lack of interest or motivation. The results for cohort 2 are markedly different. A relatively brief training regime resulted in dramatic improvements, increasing performance to normative levels. Moreover, the gains were maintained in subsequent trials during the same session and on a subsequent day. Goldberg et al. found that prompting produced only temporary gains and concluded that some schizophrenic patients are unable to learn this frontally mediated task without heroic efforts. The results of this study demonstrate that that conclusion does not extend to our subjects, who were more like the acutely ill patients found in many community hospitals.

TABLE 1. ANOVAs of Wisconsin Card Sorting Test Results for Schizophrenic Patients Given Standard Instructions and Contingent or Noncontingent Reinforcement (Cohort 1) or Contingent Reinforcement and Instructions Plus Rehearsal and Feedback (Cohort 2)

Performance Variable and Effect Analyzed[a]	Analysis of Variance F (df=1, 21)	p<
Correct responses		
Group effect	3.72	n.s.
Phase effect	10.07	0.005
Group by Phase interaction	5.58	0.05
Categories completed		
Group effect	11.73	0.005
Phase effect	7.25	0.03
Group by Phase interaction	6.85	0.03
Perseverative errors		
Group effect	0.34	n.s.
Phase effect	2.62	n.s.
Group by Phase interaction	4.95	0.05

[a] Phase 1=standard conditions, phase 2=incentives and/or training, phase 3=standard conditions, phase 4=standard conditions on the following day.

There are several possible explanations for the discrepancy between our results and those of Goldberg et al. First, our sample was small and the results could reflect chance factors. The uniformity and magnitude of the training effects argue against the (null) hypothesis that acutely ill schizophrenic patients cannot learn to perform the Wisconsin Card Sorting Test, but caution is warranted until these results are replicated. Second, the Goldberg et al. results could reflect a type II error. Their patients were severely impaired, did not respond to treatment, and were selected with the expectation that they would do poorly on the Wisconsin test. Such a sample is not representative of schizophrenic patients as a whole. Schizophrenia is a heterogeneous diagnostic category, subsuming subgroups with different etiologies and structural and functional impairments (5, 16, 17). While some subgroups may well have a dorsolateral prefrontal dysfunction, the data suggest either that this is not a universal phenomenon and/or that many patients can compensate for such an impairment. Almost 18% of our subjects exhibited normative performance on the Wisconsin Card Sorting Test without any instruction. Similarly, Braff et al. (18) reported that a less impaired (outpatient) group did not exhibit poorer performance on the Wisconsin Card Sorting Test than normal control subjects. Other studies (19) have shown inconsistent differences between schizophrenic patients, bipolar patients, and normal control subjects, and Green et al. (20) reported that a subgroup of their schizophrenic subjects were able to learn the Wisconsin sorting task. Further research is required to determine which subtypes of patients have impairments in the information processing domains required for the Wisconsin Card Sorting Test and which patients can learn to perform the task.

Another factor contributing to the difference in the results of the two studies was the training procedures employed. Goldberg et al. informed their subjects of the general rule for sorting cards and then provided prompts after each sort. Our training differed in two important ways. Rather than simply presenting subjects with a rule, we ensured learning by repeatedly probing the subjects' comprehension throughout the training and giving positive and corrective feedback when they did not demonstrate clear understanding. Thus, the subjects were forced to be active participants in the training, and we were able to ensure comprehension at each step in the procedure. Second, the initial training was reinforced (and supplemented as needed) at two different points after testing began. These two elements, active demonstration of learning and redundancy of training, have proven to be essential in social skills training and other rehabilitation programs with schizophrenic patients (21, 22).

While these hypotheses may explain why our subjects learned the card sorting task better than the subjects in the Goldberg et al. study, they do not explain why most subjects in both studies performed so poorly on what is such an easy task for normal subjects. Nine subjects in cohort 1 failed to complete more than two categories in any of the four phases, and six completed zero categories in at least two phases. This level of performance is worse than that achieved by Heaton's sample with focal frontal impairments (9); our untrained subjects also made more perseverative errors. The failure of financial incentives to improve performance in our study is consistent with the conclusion drawn by Berman et al. (7) and Goldberg et al. (8) that the poor performance is not due to lack of attention and effort. Conversely, the ability of our brief training regime to improve performance so markedly is not entirely consistent with their hypothesis concerning prefrontal impairment. It is possible that the training provided subjects a strategy with which to compensate for a prefrontal dysfunction and circumvented their inability to develop an effective problem-solving strategy. However, that seems unlikely as the training was relatively brief and did not teach a particular strategy or mnemonic for solving the task. We simply ensured that the subjects understood the general elements and requirements of the test. Apparently, this information allowed them to generate and carry out their own strategies in subsequent trials. It might also be hypothesized that poor performance on the Wisconsin Card Sorting Test results from deficits in short-term memory, but the training did not circumvent or reduce the demand on memory.

The data are consistent with a more neuroanatomically diffuse impairment that affects executive control functions, including the ability to develop a response set and follow a plan of action (19, 23). For example, patients with focal frontal dysfunction do poorly on the Wisconsin test in part because they perseverate and cannot shift when the rule for correct responses changes. In contrast, schizophrenic patients seem to respond in a relatively random manner throughout the test, with little apparent continuity from trial to trial. Their perseverative errors reflect short strings of incorrect responses followed by unpredictable shifts that do not seem to be connected to previous feedback. They seem to have no plan, rather than being unable to shift from an incorrect plan. Card sorting performance is particularly likely to be vulnerable to an impaired ability to develop a plan of action, as subjects are given no instructions and minimal feedback. Our training may have compensated for such a deficiency. (Most subjects in cohort 2 expressed appreciation and relief at finally learning what was required.) Further light could be shed on this issue by examining blood flow before and after subjects learn how to perform the card sort. If there is a prefrontal impairment, training should not result in an increase in prefrontal activation, regardless of changes in performance. If the dysfunction is in a distal brain system, improved performance should be associated with increased frontal flow.

Two other questions are raised by our data. First, it is not clear how durable or generalizable the results of training are. There was a slight (nonsignificant) decline in performance for subjects in cohort 2 during the last two phases. It is important to determine if performance gains can be maintained over time or if they are an ephemeral response to instructions. Second, our data do not indicate whether the subjects learned a generalized information processing strategy that could be applied to other tasks or if they simply learned a highly specific mnemonic. Our training was relatively brief and focused on a specific task. We did not attempt to teach a general problem-solving strategy. It remains to be seen if a more extensive training regime could produce meaningful changes in cognitive processes that affect daily living.

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Psychiatric Illness and Irritable Bowel Syndrome: A Comparison With Inflammatory Bowel Disease

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Structured psychiatric interviews and psychological self-report measures were administered to 28 patients with irritable bowel syndrome and 19 patients with inflammatory bowel disease. Significantly more of the patients with irritable bowel syndrome had lifetime diagnoses of major depression, somatization disorder, generalized anxiety disorder, panic disorder, and phobic disorder. They had significantly more medically unexplained somatic symptoms, and most had suffered from psychiatric disorders, particularly anxiety disorders, before the onset of their irritable bowel symptoms.

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Irritable bowel syndrome accounts for 13%–52% of new referrals to gastroenterology clinics (1, 2) and is a common presenting problem in primary care settings. Investigations of coexisting gastrointestinal and psychiatric symptoms in patients with irritable bowel syndrome have demonstrated that 54%–100% of these patients have mood or anxiety disorders (3–9). However, some studies did not use structured psychiatric interviewing (3, 6, 7), operationalized diagnostic criteria (3), or comparison groups (3, 4, 8), and some compared irritable bowel syndrome patients to patients without gastrointestinal illness (3, 7). The studies that did use structured interviewing (4–9) used the Research Diagnostic Criteria (RDC) (10), which prevent the diagnosis of an anxiety disorder if a primary mood disorder is discovered, so these studies underestimated the prevalence of anxiety disorders. Some studies did not reliably investigate the relative timing of gastrointestinal and psychiatric symptoms (3, 6–8), thus preventing determination of whether the psychiatric symptoms developed as a result of the medical illness, developed simultaneously with the medical illness, or were present before the appearance of gastrointestinal symptoms.

Our pilot study was an attempt to address these methodologic limitations and add to the existing knowledge about the relationship of irritable bowel syndrome and psychiatric disorders.

METHOD

We recruited subjects from our university gastroenterology clinic and family medicine clinic and from two urban private-practice gastroenterologists. The subjects were a sequential sample of patients diagnosed as having irritable bowel syndrome by a gastroenterologist after appropriate exclusion of other medical disease according to the criteria of Manning et al. (11) as modified by Thompson et al. (12). For our comparison group we selected a sequential sample of patients with inflammatory bowel disease.

Of the 63 patients in the initial sample, 47 (75%) agreed to participate, 11 (17%) refused, and five (8%) were excluded because of recent steroid use. Of the 39 patients with irritable bowel syndrome who were initially selected, most came from the university gastroenterology clinic (62%, N=24) or the private-practice gastroenterologists (31%, N=12); a small number (8%, N=3) were from the primary care clinic. A similar pattern was found in the 24 initial patients with inflammatory bowel disease: gastroenterology clinic, 54% (N=13); private practice, 25% (N=6); primary care clinic, 21% (N=5). The final sample of 47 subjects included 28 with irritable bowel syndrome and 19 with inflammatory bowel disease; the latter group comprised 13 patients with Crohn's disease and six with ulcerative colitis. Chi-square tests with Yates' correction and two-tailed t tests indicated that the groups did not differ significantly in age (mean±SD: 37.1±14.2 versus 35.3±12.5 years; t=0.44, df=45), marital status (57% versus 47% married; χ^2=0.71, df=1), social class (Hollingshead score: 3.2±0.9 ver-

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TABLE 1. Psychiatric Diagnoses of 28 Subjects With Irritable Bowel Syndrome and 19 Subjects With Inflammatory Bowel Disease

	Irritable Bowel Syndrome		Inflammatory Bowel Disease		
DIS Diagnosis	N	%	N	%	Significance[a]
Depression					
Lifetime	17	61	3	16	χ^2=7.60, $p<0.01$
Current	6	21	1	5	χ^2=1.23, n.s.
Panic disorder					
Lifetime	8	29	0	0	$p=0.01$
Current	2	7	0	0	$p=0.35$
Generalized anxiety disorder					
Lifetime	15	54	2	11	χ^2=7.32, $p<0.01$
Current	3	11	1	5	χ^2=0.02, n.s.
Panic or generalized anxiety disorder, lifetime	17	61	2	11	χ^2=9.85, $p<0.005$
Any phobia					
Lifetime	14	50	2	11	χ^2=6.20, $p<0.05$
Current	8	29	1	5	χ^2=2.61, n.s.
Agoraphobia, lifetime	7	25	0	0	$p=0.02$
Simple phobia, lifetime	8	29	2	11	χ^2=0.63, n.s.
Social phobia, lifetime	3	11	0	0	$p=0.20$
Somatization disorder, lifetime	9	32	0	0	$p=0.005$
Alcohol abuse or dependence, lifetime	9	32	3	16	χ^2=2.23, n.s.
Any lifetime diagnosis	26	93	4	19	χ^2=22.26, $p<0.000$

[a] Chi-square test with Yates' correction (df=1) or Fisher's exact test.

sus 3.0±1.3; $t=0.44$, df=45), or sex (79% versus 53% female; $\chi^2=2.41$, df=1).

All patients, including the primary care sample, were formally evaluated by a gastroenterologist and either were new patients or were returning to the clinics for follow-up care. Each patient was evaluated within 2 weeks of his or her clinic visit. Any patient using systemic steroids (excluding oral contraceptives) in the month before the interview was excluded.

After obtaining consent we interviewed the patients using an abridged form of the NIMH Diagnostic Interview Schedule (DIS) Version III-A (13), including the sections on somatization disorder, panic, generalized anxiety, phobia, major depression, and alcoholism. The DIS sections on generalized anxiety and panic disorder were modified to agree with the *DSM-III-R* criteria, and the depression section was changed so that it would elicit more accurate information about current symptoms of major depression (14). The interviewers (E.A.W., L.L., and D.A.) were trained and supervised in the use of the DIS by one of the senior psychiatrists (W.J.K.) and were blind to the gastrointestinal diagnosis. During the interview we inquired about current (during the last month) and lifetime symptoms of psychiatric disorders, and, to determine if a subject met the criteria for more than one psychiatric diagnosis, we scored the DIS to allow the maximum number of valid *DSM-III-R* psychiatric diagnoses, omitting the exclusion criteria.

Age at onset of both psychiatric and gastrointestinal illnesses and the relative timing of the psychiatric and gastrointestinal symptoms were determined by patient interview, and the medical information was confirmed by the patient's gastroenterologist.

The patients also completed a battery of self-report questionnaires, including the Hopkins Symptom Checklist-90 (15), Beck Depression Inventory (16), and the Modified Somatic Perception Questionnaire (17), a measure of somatic and autonomic perception.

Chi-square tests with Yates' correction and Fisher's exact tests were used to compare the group with irritable bowel syndrome and the group with inflammatory bowel disease on all categorical variables, such as psychiatric diagnoses and somatic symptoms. Two-tailed t tests were used to determine if the groups differed in number of symptoms or psychological test scores.

RESULTS

The psychiatric diagnoses are summarized in table 1. Compared to the patients with inflammatory bowel disease, significantly more of the patients with irritable bowel syndrome had lifetime diagnoses of major depression, somatization disorder, generalized anxiety disorder, panic disorder, and phobic disorder; 26 (93%) of the patients with irritable bowel syndrome and four (21%) of the patients with inflammatory bowel disease had at least one of these lifetime diagnoses. The difference in the prevalence of phobias was entirely due to agoraphobia. Even after we excluded generalized anxiety disorder and phobias in the irritable bowel syndrome group, 24 (86%) of the subjects had lifetime diagnoses of major depression, panic, or somatization disorder. The patients with irritable bowel syndrome also had a significantly higher mean number of DIS psychiatric diagnoses (2.25±1.50 versus 0.37±0.80; $t=5.56$, df=44, $p<0.000$). There were

TABLE 2. Psychiatric Symptoms Predating Gastrointestinal Symptoms in 28 Subjects With Irritable Bowel Syndrome

DIS Diagnosis	Patients With Earlier Psychiatric Symptoms Meeting Criteria for Diagnosis	
	N	%
Panic disorder	9	32
Generalized anxiety disorder	17	61
Phobic disorder	15	54
Major depression	10	36
Somatization disorder	9	32
Panic or generalized anxiety	18	64
Panic or generalized anxiety or phobia	22	79
Panic or generalized anxiety or major depression	18	64
Any of above diagnoses	23	82

no differences in the number of current psychiatric diagnoses per patient.

We also compared the Crohn's disease and ulcerative colitis patients and found no significant differences between them in age, sex, marital status, social status, or any psychiatric diagnosis, suggesting that, for the purposes of this study, they were a homogeneous comparison group.

From the somatization section of the DIS we found that the irritable bowel syndrome patients had a significantly higher number of medically unexplained somatic symptoms (mean±SD: 10.6±5.0 versus 2.5±2.5; $t=7.35$, $df=42$, $p<0.000$). Because abdominal distress was common in both groups, we reanalyzed the data excluding gastrointestinal symptoms, i.e., abdominal pain, vomiting, nausea, diarrhea, gas, food intolerance, and constipation; there was still a significant difference (6.1±4.2 versus 1.7±2.0; $t=4.77$, $df=42$, $p<0.000$). Since gastrointestinal symptoms are also commonly associated with anxiety disorders, we then further excluded cardiopulmonary symptoms, i.e., palpitations and shortness of breath, and continued to see a significant difference in medically unexplained somatic symptoms (5.5±3.9 versus 1.6±1.9; $t=4.52$, $df=42$, $p<0.000$).

We compared the age at onset of gastrointestinal symptoms with the age at onset of any psychiatric symptoms that met the criteria for diagnosis. Before the onset of their gastrointestinal symptoms, 23 (82%) of the irritable bowel syndrome patients had a prior history of panic disorder, generalized anxiety disorder, phobia, major depression, or somatization disorder or a combination of these disorders (table 2). Five (18%) did not report having had serious psychiatric symptoms before the diagnosis of irritable bowel syndrome. Of those five patients, three developed panic disorder, generalized anxiety disorder, or major depressive disorder after the start of the irritable bowel syndrome. Only two (7%) of the 28 patients with irritable bowel syndrome had no history of serious psychiatric symptoms either before or after development of gastrointestinal complaints.

The psychological test scores are summarized in table 3. Compared to the patients with inflammatory bowel disease, the patients with irritable bowel syndrome had significantly higher mean scores on seven of the 11 SCL-90 scales and on the Modified Somatic Perception Questionnaire but did not differ on the Beck Depression Inventory.

DISCUSSION

The results of this pilot study support the finding in prior studies (3–9) that patients with irritable bowel syndrome have a higher lifetime prevalence of psychiatric illness than patients with other serious gastrointestinal disease. We also attempted to address many of the methodological limitations of those studies.

Our sample was drawn from both primary and specialty care settings to provide a diverse patient group. Some prior studies did not use comparison groups (3, 4, 8) or used groups with disorders other than gastrointestinal disease (5, 7), with mixed inflammatory bowel disease (6, 9), with appendicitis (6), or with functional dyspepsia (9). To control for severity of illness we obtained a mix of Crohn's disease and ulcerative colitis patients, and we excluded patients using systemic steroids, which have been associated with organic psychiatric symptoms. In addition, we minimized sampling bias by not recruiting subjects with inflammatory bowel disease from colitis support groups, since these groups may contain individuals with different disease severity or help-seeking behavior.

Despite our attempt to use better methods than those in the previous studies, this investigation had a number of limitations. We excluded patients taking systemic steroids because of the possible psychotropic influence of these medications, but we may have thereby selected a healthier comparison group. Second, most of our subjects came from the gastroenterology clinic or private-practice gastroenterologists rather than directly from the primary care clinic. Patients in specialty settings have been found to have higher levels of psychopathology than primary care groups, and this difference in referrals could have introduced a selection bias. On the other hand, most of our subjects had earlier been referred to the university and private gastroenterology clinics by their primary care physicians, thus making it difficult to meaningfully separate them into primary, secondary, and tertiary care samples.

We found a surprisingly high prevalence of psychiatric disorders (93%) in the sample with irritable bowel syndrome. Although it is similar to rates found in prior studies (3–9), the magnitude of this finding may have several explanations. We determined the maximum number of diagnoses allowed by the DIS according to *DSM-III-R* criteria, whereas many former studies used the more restrictive, exclusionary RDC. Second, more than half of our subjects were

TABLE 3. Scores on Psychological Self-Report Measures for 28 Subjects With Irritable Bowel Syndrome and 19 Subjects With Inflammatory Bowel Disease

	Irritable Bowel Syndrome		Inflammatory Bowel Disease		Two-Tailed t Test		
Questionnaire	Mean	SD	Mean	SD	t	df	p
Beck Depression Inventory	7.35	7.6	4.17	6.0	1.49	42	n.s.
Modified Somatic Perception Questionnaire	8.0	6.0	4.4	5.1	2.05	41	<0.05
Hopkins SCL-90							
Somatization	59.6	9.9	52.0	9.6	2.55	42	<0.05
Obsessive-compulsive	61.1	15.0	53.3	10.4	1.89	42	n.s.
Interpersonal sensitivity	59.8	12.4	51.4	14.5	2.06	42	<0.05
Depression	61.2	11.4	55.8	9.1	1.64	42	n.s.
Anxiety	58.1	13.1	48.9	13.0	2.29	42	<0.05
Hostility	56.3	12.0	49.4	14.0	1.76	42	n.s.
Phobic anxiety	42.5	18.0	40.3	13.5	0.45	42	n.s.
Paranoia	55.3	18.2	43.9	14.8	2.20	42	<0.05
Psychoticism	56.3	18.4	45.6	14.6	2.07	42	<0.05
Global severity	60.4	9.6	51.4	8.5	3.20	42	<0.005
Positive symptom total	60.6	8.8	54.2	8.3	2.44	42	<0.05

diagnosed as having generalized anxiety disorder, a diagnosis that was unavailable to researchers using the RDC. The validity of this diagnosis in patients with irritable bowel syndrome is unknown, since the diagnostic criteria for generalized anxiety disorder state that organic factors must be excluded as a precipitant of the disturbance. The causal relationship between irritable bowel syndrome and anxiety is poorly understood, and it appears that the two disorders are reciprocal, not that one clearly precipitates the other (18). However, even with the exclusion of generalized anxiety disorder and phobias, 86% of the irritable bowel syndrome patients had lifetime psychiatric diagnoses of major depression, panic, or somatization disorder.

Although psychiatric and gastrointestinal symptoms in patients with irritable bowel syndrome have been associated in prior studies, there has been disagreement over the timing of symptoms. Could the magnitude of psychiatric disorder in irritable bowel syndrome patients be explained as a reaction to the chronic gastrointestinal distress? The relative lack of psychiatric illness in the comparison group with inflammatory bowel disease suggests that this is not the case. Despite the severity of gastrointestinal illness in the patients with Crohn's disease and ulcerative colitis, the lifetime prevalence of psychiatric disease in this group was low. Because of the small size of our comparison group we were unable to determine the relative contributions of the Crohn's disease and ulcerative colitis patients to this low prevalence figure. However, the overall prevalence agrees with findings in other studies, which have shown that the lifetime prevalence of psychiatric illness in patients with ulcerative colitis is not significantly different from the rate in patients without gastrointestinal disease (19–21) and that the rate in Crohn's disease patients may be the same (20) or slightly higher (21, 22).

In addition, the majority (82%) of our patients with irritable bowel syndrome reported that the onset of their psychiatric symptoms occurred before the appearance of gastrointestinal distress. The time from onset of psychiatric illness to development of gastrointestinal symptoms in these patients ranged from a few weeks to many years, suggesting that, although some irritable bowel syndrome patients appear to have concurrent psychiatric illnesses, such as panic disorder (23), irritable bowel syndrome may not be merely a somatic manifestation of acute psychiatric illness. Although differences between our two groups of subjects were found in lifetime psychiatric diagnoses, the patients with irritable bowel syndrome also had a high degree of current psychological distress according to the SCL-90. These data suggest that many patients with irritable bowel syndrome have intermittent *DSM-III-R* anxiety and depressive disorders and that even between major episodes they retain substantial but subclinical psychological distress. Patients with high levels of psychological distress or "negative affectivity" (those with high anxiety, depression, and hostility scores on psychological measures of distress) have been found in multiple studies to report significantly more somatic symptoms than normal subjects (24).

In addition to gastrointestinal symptoms, patients with irritable bowel syndrome have been found to have multiple other symptoms, such as headache, backache, lethargy, dizziness, dysuria, and dysmenorrhea (3, 25–28). Compared with peptic ulcer patients and normal comparison subjects, patients with irritable bowel syndrome report more frequent minor illnesses (such as colds), experience trivial illnesses as more serious, and are more disabled by them (29). During colonic balloon inflation patients with irritable bowel syndrome report pain sooner than normal subjects and in atypical sites (30–32). These findings suggest that patients with irritable bowel syndrome may amplify minor physiologic sensations. Our data from the somatization disorder section of the DIS, the Modified Somatic Perception Questionnaire, and the

SCL-90 are consistent with these findings; the patients with irritable bowel syndrome reported more minor somatic symptoms than patients with inflammatory bowel disease.

Many patients have symptoms of irritable bowel syndrome but do not report them to physicians (33). Those who do report these symptoms have higher prevalences of history of psychosocial distress (anxiety, depression, and somatization), abnormal personality patterns, poor coping skills, illness behavior, disability, and life disruption (34).

Many patients with irritable bowel syndrome appear to have a higher proportion of slow (3 cycles/min) enteric myoelectrical activity than do normal subjects, and this characteristic pattern persists despite symptom remission. These observations suggest that the combination of this myoelectrical rhythm variation and prior psychiatric illness may constitute a trait marker of enteric nervous system or CNS vulnerability to development of irritable bowel syndrome, which emerges during psychological distress (35).

The lifetime prevalence of psychiatric disorders in our patients with irritable bowel syndrome was 93%, a figure that is within the range suggested by previous studies (3–9). Our finding of a 61% lifetime prevalence of depression in this sample is similar to the 60%–70% lifetime depression rates we found in previous studies of chronic pelvic pain (36), atypical chest pain (37), chronic fatigue syndrome (38), tinnitus (39), and low back pain (40), conditions that have also been associated with chronic distress. What distinguishes irritable bowel syndrome patients from these other groups (with the exception of atypical chest pain) is the large percentage who have diagnoses of prior anxiety disorder. These anxiety disorders, thought to involve a dysregulation of autonomic nervous system function, could be associated with the development of a disorder of enteric nervous system motility. In addition, recent evidence (18) suggests that disordered motility may then result in further changes in autonomic nervous system function, thus reinforcing a cycle of reciprocally worsening anxiety and gut function.

Overall, the patients with irritable bowel syndrome in this study showed greater sensitivity to minor physical symptoms, more psychological distress, and a higher lifetime prevalence of psychiatric disorders compared with patients who had inflammatory bowel disease. These findings suggest that such patients might profit from formal psychiatric evaluation and treatment with both psychotherapeutic and psychopharmacologic modalities.

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Long-Term Predictors of Outcome in Abstinent Alcoholic Men

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Twenty-nine alcoholic men who had been abstinent for more than 2 years were evaluated behaviorally and neuroendocrinologically and then followed for 2 years. Mean length of abstinence at intake was shorter in the eight patients with histories of depression (3.3 years) than in the patients without such histories (6.8 years). Six patients relapsed during follow-up, all of whom had been sober less than 5 years. None of the neuroendocrine variables studied was predictive of outcome. In summary, abstinence of less than 5 years and comorbidity with depression were most predictive of poor outcome.

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Relapse rates for alcoholic patients are determined by many factors, such as sample studied, age, sex, past chronicity, work, interpersonal relations, severity of the alcohol dependence, and length of abstinence (1–4). Comorbidity is an additional factor (5, 6). Preliminary evidence suggests that the diagnosis of depression (7) or schizoaffective disorder (D.S. Hasin et al., unpublished data, 1989) in alcoholic patients may predict poor outcome.

Patients suffering from major depression and/or alcoholism may also show a blunted thyroid-stimulating hormone (TSH, thyrotropin) response after administration of thyrotropin-releasing hormone (TRH) (8, 9). In alcoholism, this blunted response has been found both during acute withdrawal (10) and after prolonged abstinence (11), suggesting that it may be a trait marker, at least in some patients. There is also evidence that TSH blunting may predict treatment outcome, particularly in depressed patients (8, 9, 12). To our knowledge, the relationship between TSH response and treatment outcome has not been evaluated in alcoholic patients.

To investigate whether such variables as comorbidity and the TRH test would predict outcome in long-term abstinent alcoholic men, we designed a prospective study of members of Alcoholics Anonymous (AA) who had been abstinent for more than 2 years. This design was chosen because data for most studies examining predictors of outcome have been collected during short-term abstinence from alcohol. The demographic details of this patient sample and the comparison of their neuroendocrine data to those of a normal volunteer group have already been reported (11). We now present a more detailed analysis of the outcome data.

METHOD

We studied 29 male AA members aged 30 to 66 years (mean±SD=49.6±11.2). During the initial interview careful personal and family histories were taken, and diagnoses were made according to the Research Diagnostic Criteria (RDC) (13) and *DSM-III*. Each patient had a diagnosis of alcohol dependence, in remission (*DSM-III* code 303.93). All patients had been diagnosed as alcoholic during previous hospitalizations and had achieved abstinence from alcohol for at least 2 years by joining a local AA group. Some patients had histories of depression, but in each case the depression had been preceded by the diagnosis of alcoholism. None had been hospitalized for depression, and none was depressed or was being treated for depression during the study. All patients had started to drink between the ages of 15 and 25 years and thus fulfilled Cloninger's criteria for type II alcoholism (14).

After intake, the patients were followed up for at least 2 years. Follow-up information for this study was obtained every 6 months by using standard psychiatric evaluation techniques. Follow-up data were also obtained from the AA group (outside the standard follow-up), usually when a patient unexpectedly had taken a drink. Such information triggered an immediate appointment of the patient with the physician (P.T.L.). We recorded both length of sobriety before intake and rate of relapse during follow-up. "Sobriety" or "abstinence" was defined as no evidence of

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RDC alcoholism symptoms. "Relapse" was defined as any occurrence of RDC alcoholism symptoms during follow-up.

Each patient received an injection of 0.5 mg of TRH between 8:00 and 9:00 a.m. in a standard fashion. Serum samples were frozen at −20 °C, and duplicate samples were assayed in the same run, as described previously (10, 11). The intra-assay coefficients of variance were as follows: TSH, 5.2%; prolactin, 8.5%; human growth hormone (GH), 4.2%; L-triiodothyronine (T_3), 5.0%; free thyroxine (T_4) index, 4.9%; reverse T_3, 15%; cortisol, 4.7%; and testosterone, 5.0%.

The baseline and response data of various subgroups were compared by means of Student's t tests. Logarithmic transformations were performed when necessary, and separate variance estimates were used when the data were found to be heterogenous. McNemar's test and the chi-square test were also used (15).

RESULTS

All 29 patients by definition had been abstinent from alcohol for at least 2 years. Eight (28%) had personal histories of depression, five (19%) of 27 had family histories of depression, and 22 (81%) of 27 had family histories of alcoholism. No family data were available from two patients. During the 2-year follow-up period, six (21%) of the 29 patients relapsed. In each case, relapse was defined as reemergence of drinking.

Psychiatric History and Endocrine Variables

Table 1 summarizes the relationships between personal history of depression and other variables. As shown there, length of abstinence was approximately 50% shorter in patients with personal histories of depression than in patients with no such history. Seven (88%) of the eight patients with histories of depression had been sober less than 5 years. In contrast, there were no differences in any neuroendocrine variable, including TSH response, between patients with and patients without histories of depression. Because there was no age difference between groups and because all patients started drinking between the ages of 15 and 25 years, the patients with histories of depression were not likely overall to have experienced the onset of alcoholism more recently.

Patients with family histories of depression also showed a shorter duration of sobriety than patients without such histories (mean±SD=3.6±1.8 versus 6.6±6.4 years, respectively), although this difference did not reach statistical significance. A family history of alcoholism had no effect on length of abstinence (5.9±6.2 versus 6.6±5.0 years). Thus, comorbidity (but not family history of alcoholism) powerfully reduced the likelihood of sustained abstinence.

There was no clear association between a personal or family history of depression and TSH blunting (table 2). Of the nine patients with TSH blunting, defined as Δ_{max} TSH<5 µU/ml, two (22%) had personal histories of depression, two (22%) had both personal and family histories of depression, and five (56%) had no history of depression. Similarly, there was no association between a family history of alcoholism and TSH blunting. Seven (78%) of the nine patients with TSH blunting had such family histories, as did 15 (83%) of 18 patients with normal TSH responses.

TABLE 1. Neuroendocrine Variables in 29 Men Abstinent From Alcohol for at Least 2 Years Who Did or Did Not Have Histories of Depression

	Without History (N=21)		With History (N=8)	
Variable	Mean	SD	Mean	SD
Age (years)	49.8	11.9	49.3	11.3
Sobriety (years)[a]	6.8	6.5	3.3	1.5
TSH (µU/ml)				
Baseline	2.5	0.6	2.4	1.3
Peak	11.6	[illegible]	8.4	4.7
Change	9.1	4.9	6.0	3.5
Prolactin (ng/ml)				
Baseline	5.9	2.6	6.0	1.8
Peak	28.4	14.2	36.7	28.2
Change	22.6	14.3	30.7	28.0
Baseline GH (ng/ml)	1.1	0.7	1.2	0.5
Free T_4 (U)	6.6	1.5	6.4	1.7
Total T_4 (µg/dl)	7.5	1.7	7.0	1.7
T_3 (ng/dl)	130	35	139	26
T_3 uptake (%)	44.9	4.8	46.1	3.7
Reverse T_3 (ng/dl)	19.3	7.4	18.0	8.3
Cortisol (µg/dl)	11.2	3.5	9.3	4.7
Testosterone (ng/ml)	5.2	2.3	5.2	1.9

[a] Significant difference between groups (t=2.31, df=24.51, $p<0.03$; Student's t test).

Length of Sobriety and Endocrine Variables

The 16 patients who had been sober for less than 5 years were compared to the 13 patients who had been sober for 5 years or more. The short-term sobriety group had been abstinent for 2.3±0.5 years (mean±SD), compared to 10.1±6.5 years for the long-term sobriety group (t=4.30, df=12.11, $p<0.001$; Student's t test). The mean ages of the two groups were similar (46.8±11.3 versus 53.1±11.3 years). There were no between-group differences in mean serum levels of TSH, prolactin, GH, free T_4 index, total T_4, T_3, reverse T_3, T_3 uptake, cortisol, and testosterone. There also was no clear association between duration of abstinence and TSH blunting. Six of the nine patients with TSH blunting had been sober less than 5 years, and the remaining three had been sober 5 years or more. The nine patients with TSH blunting had been abstinent for 5.0±1.4 years, and the 20 patients without blunting had been abstinent for 5.2±1.5 years. However, the T_3/T_4 ratio was significantly lower in patients with long-term sobriety (20.8±6.2 versus 16.8±3.0; t=2.19, df=20.99, $p<0.04$). Further anal-

TABLE 2. History of Depression, TSH Response, and Outcome in 29 Men Abstinent From Alcohol for at Least 2 Years[a]

Patient	Age (years)	Length of Sobriety (years)	Family History of Depression	Δ_{max} TSH (μU/ml)	Relapse During 2-Year Follow-Up
History of depression					
1	64	3	Yes	2.1	No
2	38	6	Yes	7.2	No
3	44	5	Yes	4.5	No
4	60	3	No	12.3	No
5	51	2	No	3.6	Yes
6	53	2	No	9.8	No
7	30	2	No	3.0	No
8	54	3	No	6.0	No
No history of depression					
9	50	8	No	14.7	No
10	62	29	No	6.5	No
11	58	2	—[b]	8.6	Yes
12	59	14	No	3.9	No
13	60	7	No	19.1	No
14	57	13	No	17.4	No
15	39	7	No	10.0	No
16	66	8	No	6.6	No
17	45	3	—[b]	13.1	Yes
18	43	3	No	13.6	No
19	54	2	Yes	6.6	No
20	34	2	No	3.3	No
21	40	2	No	6.9	No
22	34	2	No	5.6	Yes
23	57	14	No	7.7	No
24	26	2	No	2.7	No
25	60	8	No	5.0	No
26	66	7	No	4.7	No
27	49	2	No	4.2	Yes
28	54	2	Yes	7.8	Yes
29	32	5	No	16.6	No

[a] Each patient had a primary diagnosis of alcohol dependence, in remission (*DSM-III* code 303.93). Each case of depression was secondary to alcoholism; no patient had been hospitalized for depression.

[b] Family history not available.

ysis of these data suggested that the difference in T_3/T_4 ratio was due to steadily declining T_3 levels during sobriety (serum T_3 versus years of sobriety: $r=-0.42$, $df=28$, $p<0.03$; Pearson's product-moment correlation). Moreover, although there was no significant difference in age between the groups, age correlated significantly with years of sobriety ($r=0.40$, $df=28$, $p<0.03$).

Relapse and Baseline Variables

During the 2-year follow-up period, six patients (21%) relapsed and 23 patients remained abstinent. The age difference between the two groups was not significant (48.5±8.4 versus 49.9±12.4 years, respectively). However, those who relapsed had been abstinent for a shorter time than those who did not relapse (2.2±0.2 versus 6.7±1.3; $t=3.51$, $df=22.71$, $p<0.002$). Further analysis of the data revealed that six (38%) of the 16 patients who had been abstinent less than 5 years relapsed, as compared to none of the 13 patients who had been abstinent 5 years or more ($\chi^2=6.15$, $df=1$, $p<0.02$). None of the neuroendocrine variables studied was predictive of treatment outcome. The TSH responses of the two groups were similar (8.3±5.0 versus 8.3±3.5 μU/ml).

DISCUSSION

This study is an extension of earlier work with alcoholic patients who were studied both during acute withdrawal (10) and after prolonged abstinence (11). We now have presented the outcome data gathered from the latter group.

In the sample reported on here, two factors determined length of sobriety: comorbidity with depression and length of abstinence. A personal history of depression negatively affected length of abstinence at intake; the latter, in turn, powerfully predicted relapse during the 2-year follow-up. The relapse rate among patients sober less than 5 years was high (38%); there was no relapse in patients sober for 5 years or longer. Depression is rather common in abstinent alcoholics. Behar et al. (5), studying 72 patients who had abstained for a mean of 64 months, found that 15% had serious, debilitating depressive illness. The comorbidity of alcoholism and depression has been addressed (6), but the literature reveals little about the effects of depression on sustained abstinence. Hatsukami and Pickens (7) reported that, of alcoholics who had received treatment 12 months previously, those who continued to abstain had a rate of depressive symptoms of 16%, as compared to a rate of 33% in those who restarted their alcohol abuse. Thus, a diagnosis of depression negatively affected outcome. Hasin et al. (unpublished findings) also noted that a diagnosis of schizoaffective disorder predicted poor outcome.

Although mental health professionals are well aware that length of abstinence from any addictive drug or substance may be an important factor determining outcome, most data on alcoholics have been collected during short-term abstinence. Achievement of 1 or even 6 months of abstinence is a poor predictor of stable abstinence (1, 2). Vaillant and Mildofsky (3) reported that relapse also was not uncommon after even a year of stable abstinence. Our data support this observation and at the same time provide important additional information: the rate of relapse after 2 years of abstinence was still 38%, but it fell to 0% after 5 years of abstinence. Relapse rates in alcoholic patients, of course, are determined by many factors, such as sample studied, comorbidity, age, sex, past chronicity, work, interpersonal relations, and severity of the alcohol dependence (1–4). It is also possible that patients with sustained abstinence constitute a subgroup that for various reasons (e.g., personality structure, severity of illness, previous chronicity of illness, environmental support) could be considered at lower risk for relapse. The data presented here do not provide answers to these questions. In summary, little is known about the relationships between diagnosis of depression, length of abstinence, and long-term risk for relapse in the alcoholic. For example, what can we tell our patients about their risk for relapse after they have been sober for 1 year? Moreover, do we need to treat depression in our alcoholic patients early and aggressively to improve outcome?

There was a significant difference in the T_3/T_4 ratio between patients who had been sober less than 5 years (mean=2.3 years) and those who had been sober for 5 or more years (mean=10.1 years). The T_3/T_4 ratio is a sensitive measure of the amount of T_4 secreted by the thyroid gland in comparison to the amount of T_3 derived from T_4. It has been estimated that approximately 80% of T_3 is derived by metabolic deiodination of T_4 to T_3 in peripheral tissues, including the liver (16). Further analysis suggested that this finding was mainly due to steadily decreasing serum T_3 levels during sobriety. Reduced serum T_3 levels have been noted in humans with increasing age (16); the finding may thus have been due to the greater age of the patients who had been abstinent longer (a significant association between age and years of sobriety was noted in this sample). Several groups of investigators have demonstrated a relationship between TSH blunting and treatment outcome in depressed patients (8, 9, 12), although most used a different study design, in which the change in $\Delta_{\max}$ TSH between first (pretreatment) and second (posttreatment) testing was calculated and related to outcome. No such relationship was observed in our sample. Nine patients showed TSH blunting, and the distributions of this abnormality in the groups with short-term and long-term sobriety were about equal. Moreover, the study reported here addressed alcoholic rather than depressed patients. The lack of a demonstrable relationship between TSH blunting and outcome is thus not directly comparable to findings in other reports in the literature.

Taken together, the neuroendocrine data presented here do not reveal differences in serum levels of hormones of the hypothalamic-pituitary-thyroid axis (other than the T_3/T_4 ratio) between patients who have been sober less than 5 years and patients who have been sober for 5 years or longer. Our previous report (11) indicated marked differences in serum levels of these hormones between abstinent alcoholic patients and normal subjects. For example, abstinent alcoholics showed 1) a "euthyroid sick syndrome," evidenced by low levels of reverse T_3 and normal levels of T_4, 2) greater binding capacity for thyroid hormones, evidenced by a lower T_3 uptake value and a higher level of T_4-binding globulin, and 3) TSH blunting in 31% of the patients. Our data strongly suggest that (with the possible exception of the T_3/T_4 ratio, which was largely due to declining T_3 levels) no further changes in hormone levels can be expected after 2 years of sobriety. Finally, length of abstinence and diagnosis of depression, but not the neuroendocrine tests used, were predictive of outcome. The complex associations between length of sobriety, diagnosis of depression, and outcome deserve further study.

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Sudden Death From Acute Cocaine Intoxication in Virginia in 1988

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A review of medical examiners' autopsy records revealed that in 1988, 33 residents of Virginia died of acute cocaine intoxication. The subjects were 19 to 45 years old; most were men, used cocaine intravenously, and used other toxic substances with the lethal dose of cocaine.

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The medical sequelae of cocaine abuse receive more attention as cocaine use increases. The most serious adverse effect is sudden cardiac death. Myocardial infarction may arise shortly after cocaine use, even among those without coronary artery disease (1). Coronary artery spasm (2) and other cardiac complications (3) may occur with small doses of this drug. Cardiac findings of coronary artery disease, left ventricular hypertrophy, inflammation, fibrosis, and contraction banding, and intracranial hemorrhage may be present in cases of death from cocaine intoxication (4–6).

We report patterns of cocaine deaths in Virginia in 1988. Factors studied included preexisting cardiovascular abnormalities, method of drug use, serum concentrations of cocaine and benzoylecgonine, and toxicologic evidence of other substances.

METHOD

We reviewed the autopsy records of the Virginia Chief Medical Examiner for 1988. The population of Virginia was 6,068,000, and 43% were in the age range 19–45 years. On the basis of post-mortem toxicologic findings, clinical history, or both, we found 33 nontraumatic and nonhomicidal deaths that were due to cocaine intoxication. We confirmed the presence of intravenous cocaine use by autopsy findings of needle punctures not due to cardiopulmonary resuscitation. Tabulations included age, race, and sex; we also recorded heart weight and evidence of coronary artery disease (greater than 70% narrowing of at least one major coronary artery) and myocardial fibrosis.

Toxicologic studies were done in one of four regional centers (Falls Church, Richmond, Roanoke, and Norfolk). One center did not measure serum concentration of benzoylecgonine. After spontaneous hydrolysis of cocaine, benzoylecgonine appears in the serum and may remain there for at least 72 hours. Therefore, it may represent acute, subacute, or recurrent cocaine exposure. Although pseudocholinesterase converts cocaine to ecgonine methyl ester (7), this metabolite was not measured. Thus, serum cocaine and benzoylecgonine levels incompletely quantify the degree of cocaine intoxication.

RESULTS

Two-thirds of the subjects were white (table 1). Women tended to be younger than men (mean±SD age=25.5±4.4 versus 31.7±6.2 years; t=1.92, df=31, p=0.06, two-tailed t test). As expected, the mean heart weight of women was less than that of men (277.5 ±75.9 versus 418.3±70.2 g; t=3.73, df=31, p=0.001). There was no statistically significant relationship between heart weight and race or age.

Morphine had been used with cocaine in 10 cases (table 1), and diazepam in one case. Concomitant alcohol intoxication was common.

Although no serum cocaine level is universally lethal, our subjects' levels fell into the range reported by Wetli and Wright (8) (0–26.0 mg/liter). Similarly, variations in drug tolerance due, in part, to habituation make it difficult to define lethal morphine levels. The morphine values we report are below or in the lower end of the toxic range (9). The ethanol concentrations found in the subjects in the present study are more consistent with mild to moderate than lethal intoxication.

There were physical findings of acute or subacute intravenous drug use in two-thirds (N=22) of the subjects; these findings were less common among the women than the men. Three of these subjects and one nonintravenous drug user had ingested large amounts

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TABLE 1. Demographic and Clinical Data on 33 Subjects Who Died of Acute Cocaine Intoxication in Virginia in 1988

						Serum Levels			
Patient	Age (years)	Race	Sex	Intravenous Drug Use	Heart Weight (g)	Cocaine (mg/dl)	Benzoyl-ecgonine (mg/dl)	Alcohol (mg/dl)	Morphine (mg/dl)
1	27	Black	F	No	280	0.17	0.40	230	1.36
2	39	White	M	Yes	400	0.10	0.20	80	0.10
3	31	Black	M	No	450[a]	12.00	9.00	110	0.00
4	20	White	M	Yes	425	2.60	5.80	10	0.00
5	36	Black	M	Yes	350	0.38	4.80	10	0.07
6	32	White	M	Yes	400	0.60	3.00	0	0.00
7	24	White	M	Yes	370	9.00[b]	10.00	0	0.00
8	29	White	M	Yes	510	0.75	7.40	0	0.00
9	32	White	M	No	500	0.10	1.10	180	0.00
10	30	Black	M	No	420	0.10	4.40	0	0.00
11	40	White	M	Yes	500	0.00	0.50	130	0.10
12	28	Black	F	Yes	200	0.05	0.20	310	0.45
13	28	White	F	No	380	9.40	—	40	0.00
14	29	Black	M	Yes	420	1.10	—	0	0.00
15	19	White	F	No	250	10.10	—	0	0.00
16	32	White	M	Yes	400	13.10	—	0	0.00
17	45	Black	M	Yes	320	2.80	—	10	0.00
18	33	Black	M	No	400	26.10[b]	—	0	0.00
19	25	White	M	Yes	350	0.10	—	0	0.23
20	30	White	M	Yes	390	2.60	—	10	0.00
21	36	White	M	No	500	9.10	—[c]	30	0.00
22	25	White	M	No	430	0.18	0.22	10	0.00
23	38	White	M	Yes	250	3.82	9.48	0	0.00
24	33	White	M	Yes	510	0.17	0.08	230	0.02
25	37	White	M	Yes	550[a]	1.87	7.19	20	0.00
26	22	White	M	Yes	330[d]	4.19[b]	30.66	10	0.00
27	42	Black	M	Yes	490[a]	0.41	3.15	30	0.02
28	31	White	M	Yes	450	27.64[b]	11.61	0	0.00
29	21	Black	M	Yes	350	0.18	2.28	0	0.17
30	28	Black	M	No	330	0.04	0.10	70	0.00
31	32	White	M	Yes	460	0.54	0.87	0	0.27
32	38	White	M	No	470[d]	0.04	4.42	0	0.00
33	30	White	M	Yes	405	3.37	12.96	0	0.00

[a] Myocardial fibrosis.
[b] Had plastic bag of cocaine in gastrointestinal tract.
[c] Urine positive for benzoylecgonine.
[d] Critical stenosis of at least one major coronary artery.

of cocaine before dying; they accounted for four of the five highest cocaine and benzoylecgonine levels reported. Autopsy reports did not mention intranasal inhalation or "crack" smoking as possible types of cocaine use.

Two subjects had coronary artery disease and three subjects had myocardial fibrosis. There was no relationship between these findings and age, race, manner of administration, or serum intoxicant level. There was no pattern of congenital coronary artery anomaly that might have predisposed our study sample to sudden death from heart disease.

There were also post-mortem findings of broken plastic cocaine bags in the gastrointestinal tract.

DISCUSSION

The youth of our study sample probably accounts for the paucity of heart disease found at autopsy. In contrast, Mittleman and Wetli (4) attributed 15 of 24 cocaine-related deaths to coronary artery disease. Their subjects ranged in age from 29 to 71 years, and most were older than 40. The heart weights, cocaine levels, and sex ratio of their study sample were similar to ours. Tazelaar et al. (6) also found a low prevalence of heart disease in a somewhat young (mean age=33.4 years) group of subjects who died from cocaine intoxication. In our study, Virginia medical examiners did not comment on the presence or absence of myocardial contraction bands so common in the study of Tazelaar et al.

One Virginia subject who had died of cocaine intoxication had staphylococcal endocarditis complicated by intracerebral hemorrhage. We did not include her in our study because her death was only remotely related to cocaine use. In a study sample smaller than ours, Mittleman and Wetli (4) found intracerebral hemorrhage in five subjects. Age-related variations in the prevalence of hypertension and variations in death reporting practices may explain these differences.

Three of our subjects had myocardial interstitial fibrosis; this rate is similar to that reported by Tazelaar et al. (6). Still, none had myocardial cellular infiltration, as described by Virmani et al. (5). Many of their subjects with cellular infiltration were homicide victims with low serum cocaine levels. In the present study, serum cocaine and benzoylecgonine levels of subjects with coronary artery disease or myocardial fibrosis did not differ from those of subjects with normal hearts. Therefore, we cannot assert that these cardiac disorders are "permissive" or lower the threshold for sudden death from cocaine use. The somewhat low prevalence of these disorders neither proves nor disproves a causal connection with chronic cocaine exposure. Our understanding of the cardiac effects of acute, subacute, and chronic cocaine use is incomplete, in part because unknown substances may be mixed with cocaine.

Multiple factors prevent the precise quantification of cocaine intoxication. These include variations in time between death, autopsy, and serum analysis; the instability of cocaine in the blood; the complexities of its metabolites; and accompanying known or unknown toxins. Hypertension and tachycardia from combined use of cocaine and alcohol may contribute to sudden cardiac death in some subjects (10). Testing the inverse relationship between cocaine and alcohol levels in our data did not confirm Ayd's hypothesis (10) that alcohol intoxication lowers the threshold for sudden death from cocaine use.

Most of our subjects used cocaine intravenously. Rapid increase of blood cocaine concentration leads to prompt stimulation of the sympathetic nervous system; therefore, inhalation of cocaine (crack) might be fatal more often than would similar amounts of cocaine taken orally or intravenously. We cannot prove this hypothesis, however, because autopsy reports did not describe crack use.

Absorption of cocaine from ruptured plastic bags in the gastrointestinal tract produced very high blood levels of cocaine in our study. We cannot describe this practice as uniformly or usually lethal, however, because we do not know how many subjects transport cocaine in the gastrointestinal tract or the prevalence of bag rupture.

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Koro: Proposed Classification for *DSM-IV*

Ruth L. Bernstein, M.D., and Albert C. Gaw, M.D.

Koro, a culture-specific disorder consisting of complaints of genital retraction and fear of death associated with genital retraction, has been recognized in Asian cultures in single cases and in epidemic proportions. Koro has been described in non-Asian patients as well, leading to debate concerning the true nature of the syndrome. The authors review past attempts to define and classify koro and present a classification for DSM-IV *that they believe could be used to classify other culture-bound syndromes as well.*

(Am J Psychiatry 1990; 147:1670–1674)

Koro, a culture-specific psychiatric disorder that has existed for centuries in Asian cultures, was first described for Western science in 1895 (1). It is manifested by acute anxiety associated with the fear of genital retraction and is usually accompanied by the thought that complete disappearance of the organ into the abdomen will result in death. Many cases of the syndrome have been described in Southeast Asia, sometimes in epidemic proportions. Numerous case descriptions of koro-like phenomena in non-Asian subjects also exist, leading to speculation that koro may not be a truly culture-bound syndrome.

Given the existing confusion concerning koro, we believe it essential that a definitive classification be established for this syndrome. *DSM-IV*, aspiring to international status, should attempt to include some description of this and other culture-related syndromes. In view of the increase in worldwide travel and immigration, more of these syndromes, now considered rare in Western countries, may emerge in the United States and other industrialized societies. In this paper, we report a case of koro in Boston, review attempts to describe the syndrome, and propose a classification scheme for *DSM-IV*.

CASE REPORT

The patient was a 25-year-old Cantonese waiter who was referred by his primary physician for the chief complaint of pain in the penis and insomnia, which began following intercourse with a prostitute 1 month before the referral. After his visit to the prostitute, the patient thought he was exposed to cold weather on the way home. Then, over a 3-day period, he experienced intermittent burning pain in his penis. While at work, he experienced a sudden, burning pain accompanied by the fear that his penis was shrinking. The patient became frightened, concerned that he might die if his penis shrank into his abdomen. He developed palpitations and anxiety. Over the next few days, he tried to masturbate to assure himself that his penis was not shrinking. On one occasion, he was unable to achieve an erection and began to panic, fearing that he had developed *suk-yeong* illness.

Local physicians could not substantiate any urinary tract pathology. Prescribed analgesics and tranquilizers did not alleviate his symptoms. His continuing distress prevented him from working. He was afraid to go to sleep for fear of dying. On consulting his elders in Chinatown, the patient was told he was afflicted with a rare disease. Desperate and unable to sleep, he began to develop suicidal ideation.

The patient, described by his mother as timid, was born in Canton and migrated to Hong Kong with his family at age 10. He started masturbating at age 13. While in China and Hong Kong, he heard that a man would die if his penis retracted into his abdomen. The patient denied having had sexual intercourse before coming to the United States and acknowledged that his recent contact with a prostitute was his first.

HISTORICAL REVIEW

The term "koro," although of uncertain origins, is believed to come from a Malaysian word meaning tortoise (2). Koro is found primarily in Southeast Asian cultures. When first introduced to Western science, the malady was thought to be indigenous to southern Celebes (Sulawesi), an island of Indonesia (1). However, ancient Chinese medical books have described *suo-yang* (retraction of the genitals into the abdomen) as a fatal disease (3). The syndrome of koro is still known as *suk-yeong* among Cantonese-speaking Chinese and *suo-yang* among Mandarin-speaking Chinese. Koro is reported primarily among Chinese of the southern coast of China (Kwangtung [Guangdong] and Fukien [Fujien] provinces) and among Chinese in Southeast Asia (Singapore and Malaysia) who orig-

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inally came from the southern coast of China (4). Since Gwee (3) and Yap (5) used the term in their reports, "koro" has gained acceptance as a label for a patient's fear of penile shrinkage as well as for the rarer female complaint of labial and breast hyperinvolution.

PREVALENCE

Isolated occurrence of koro is rare. Yap (5) was able to compile only 19 cases in 15 years. Nonetheless, koro in epidemic proportions has been described (4, 6–12). Ngui (6) reported an epidemic in Singapore in 1967 following a rumor that infected pork was causing the disorder. Suwanlert and Coates (11) described more than 1,000 cases that occurred in Thailand shortly after the Vietnam conflict. Tseng et al. (4) described two large epidemics that occurred in Kwangtung (Guangdong), China. The first, involving more than 2,000 subjects, occurred in 1984–1985, and the second occurred in 1987. Tseng et al. discussed how these epidemics were induced by the cultural attitudes of the people in that region, specifically the common folk belief in evil-induced genital retraction and the belief that ghosts of the dead (who have no penises) disguised themselves to steal penises from the living. The community's anxious reaction and the hysterical atmosphere facilitated and perpetuated the epidemics.

CULTURAL CONSIDERATIONS

The occurrence of this syndrome in epidemic proportions underscores that koro is a culture-bound syndrome. It appears obvious that the cultural belief in the concept of koro is an important factor in the genesis of the syndrome, yet the question of whether koro is a unique cultural syndrome or merely the cultural expression of a universal phenomenon has been raised. Indeed, Kraepelin (13) mentioned shrinkage of the penis among the hypochondriacal delusions to be found in depressive states. Western thinking has long classified koro from a psychoanalytic perspective as acute castration fear (14). Simons (15) argued that many men experience the sensation of genital shrinkage. In societies in which the belief in koro is endemic, the sensation generates anxiety, which in turn can cause a reduction in blood to the extremities, causing further shrinkage of the penis and further anxiety. Simons described this sequence as a "self-incriminating causal loop." Since the originating experience is found universally, he said that similar koro-like states occur in non-Asian subjects "whenever the cognitive state of subjects for any reason generates anxiety sufficient to drive the loop." A number of investigators (16–22) described cases of koro-like syndromes in individuals who had never been exposed to Chinese culture. Jilek and Jilek-Aall (23) pointed out that high rates of koro have been found in completely different cultures. They cited the 1982 koro epidemic in India that occurred among various Hindu and Muslim populations who had never been exposed to traditional Chinese medicophilosophical concepts. The thesis of Jilek and Jilek-Aall was that koro occurs in a population whose procreative capabilities are threatened by another, hostile population.

Clearly, given the right cultural setting and stimulus, koro can occur in cultures other than Chinese. Nevertheless, the epidemiology of koro shows it to be a predominately Eastern phenomenon. The afflicted individuals seem to be as influenced by social and cultural stresses as by intrapsychic phenomena. This is consistent with Eastern philosophical perspectives, which are more focused on the group than the individual. Although koro may not be uniquely Chinese, the vast majority of cases are culturally determined.

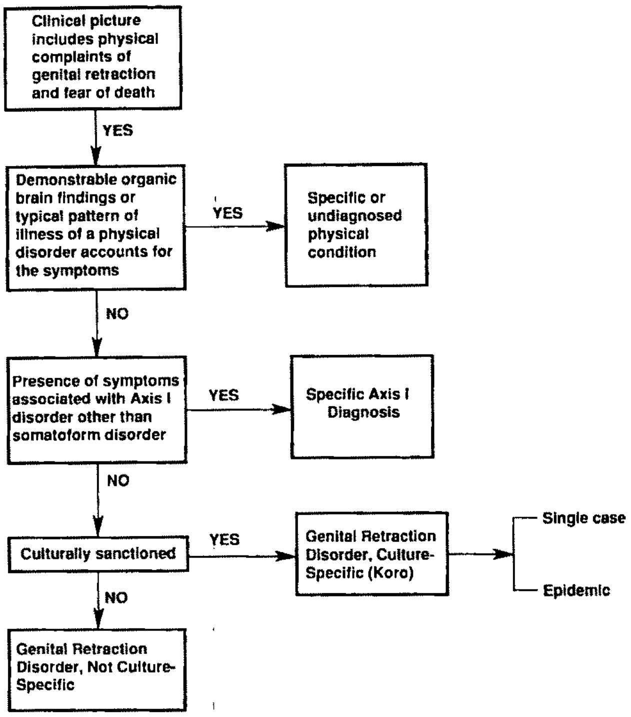
ATTEMPTS AT DEFINITION

The speculations of what primary disorder koro might represent have also been numerous. Oyebode et al. (24) demonstrated that the conviction that one's penis is shrinking can actually induce a reduction in penile circumference and therefore indicates that the koro belief in penile shrinkage is not delusional per se. In 1965, Yap (5) discussed the interpretations by different investigators of koro as anxiety neurosis, acute castration fear, and psychosis and concluded that it is a "culture-bound depersonalization syndrome." In an attempt to examine koro from an analytic perspective in the context of Chinese culture, Rin (25) attributed the phenomenon to castration fear occurring in association with oral deprivation. Gwee (3) described koro as an "acute hysterical panic reaction, brought on by auto- or hetero-suggestion and conditioning by the cultural background." In their report of 15 cases of koro-like states in non-Chinese subjects, Berrios and Morley (16) noted that all of the patients suffered from primary psychiatric disorders, some of which included agoraphobia, panic attacks, anxiety states, schizophrenia, depression, and drug abuse. They also noted, in contrast to the Chinese belief, that in all but two of the cases, the patients did not believe that the genital retraction would eventuate in death. Cases rarely have been described in persons without a primary psychiatric disorder or a cultural influence (21). Simons (15) attempted to resolve the problem of defining koro by using a purely descriptive term—the genital retraction taxon. The fact that koro-like symptoms have been associated with drug withdrawal, brain tumor, epilepsy, and syphilis has led to speculation that koro has a primary physiological substrate. Because of this, Simons suggested that all cases of the genital retraction syndrome be grouped under one category. Edwards (2) proposed that genital retraction syndromes include all the different koro-like syndromes, including koro, and that use of the culture-specific term "koro" be restricted to the cultural area where it is used.

PROPOSED CLASSIFICATION

We believe that any scheme to classify koro fully must take into consideration the following issues: 1) whether the disorder of genital retraction is a primary psychiatric disorder or is caused by another disorder, 2) whether the disorder occurs in a specific cultural context, and 3) whether the disorder occurs in an individual or in the context of an epidemic. A review of the literature reveals that the majority of culturally sanctioned cases of koro are primary psychiatric disturbances but that genital retraction complaints divorced from a specific cultural context are almost always caused by another, more pervasive psychiatric condition or by an organic disease. Therefore, one must differentiate culture-specific cases of koro from koro-like states. Furthermore, a person influenced by a folk belief in koro should not be considered psychotic or delusional, unless this person's ego functions are severely impaired. The presence of a folk belief in koro or other culturally shared beliefs is a key factor in understanding the koro phenomenon as well as in elucidating the genesis and perpetuation of koro epidemics. It is this relation to the cultural set which makes koro distinctive and its presentation dramatic. To allow clear and adequate consideration of this cultural factor, the concept of a culture-specific disorder would have to be added in *DSM-IV*, since this category is clearly missing. The concept of koro occurring in the context of an epidemic should be added to fully describe the setting in which some classical cases of koro occur. This manner of classification adds a dimension to *DSM-IV* that *DSM-III-R* neglects—a designation that the manifestations of certain psychiatric conditions are clearly dependent on a specific cultural setting.

FIGURE 1. Proposed Decision Tree for Koro in *DSM-IV*


Clinical picture includes physical complaints of genital retraction and fear of death
YES
Demonstrable organic brain findings or typical pattern of illness of a physical disorder accounts for the symptoms
YES
Specific or undiagnosed physical condition
NO
Presence of symptoms associated with Axis I disorder other than somatoform disorder
YES
Specific Axis I Diagnosis
NO
Culturally sanctioned
YES
Genital Retraction Disorder, Culture-Specific (Koro)
Single case
Epidemic
NO
Genital Retraction Disorder, Not Culture-Specific

PROPOSAL FOR *DSM-IV*

How would koro fit into *DSM-IV*? Several possibilities exist. Kaplan and Sadock (26) classified it as an atypical psychosis. Hughes (27) suggested it be included in the diagnosis of atypical somatoform disorder, panic disorder, and/or sexual disorder not otherwise specified. Tseng et al. (4) and Edwards (2) classified it as genital retraction panic disorder. Yap (5) called it a depersonalization disorder. Others may even consider it a conversion reaction. It is important to note that the cardinal feature of the koro complaint is not anxiety but genital retraction and the resultant fear of death. Panic or anxiety invariably ensue when individuals become fearful that they will be permanently altered or even die. Thus, from a descriptive standpoint, a complaint of genital retraction represents a physical symptom suggesting a physical disorder for which there are no demonstrable organic findings and which is presumed to be psychogenic in origin. For this reason we feel that koro fits most accurately in the category of somatoform disorders. However, the unique presentation of the syndrome does not fit well into any of the existing subsets of the somatoform disorders. Therefore, we propose a new subset—genital retraction disorder—with a special designation to indicate that koro (or *suk-yeong*) is culture-specific. Whether the symptoms occur in an individual or in the context of an epidemic should further be specified.

The description of koro proposed for *DSM-IV* is presented in appendix 1. The diagnostic criteria for genital retraction disorder are as follows:

A. A feeling of overwhelming panic associated with the sensation of or belief in genital retraction.
B. A fear of impending death, should the genitals be allowed to fully retract.
C. A tendency to prevent retraction by holding onto the penis, enlisting help in doing so from friends or relatives, or using devices attached to the penis.
D. Aside from the belief and its ramifications, behavior is not obviously odd or bizarre.
E. Has never met criterion for any axis I disorder other than somatoform disorder, and it cannot

be established that an organic factor initiated and maintained the disturbance.

Specify type:

In a cultural context or not in a cultural context. Single case or epidemic.

In keeping with the philosophy of *DSM-III-R,* we have formulated a decision tree for the classification of koro (see figure 1). First, underlying organic diseases such as a genitourinary disorder or an organic brain disorder must be ruled out when a patient has the chief complaint of genital retraction. Second, one should ascertain that the complaint is not part of an existing, more pervasive axis I disorder other than a somatoform disorder. Patients should be assigned the diagnosis of genital retraction disorder only after other primary axis I disorders are excluded. Third, a determination should be made as to whether a culturally sanctioned belief is present that may have caused the symptom; diagnosis of culture-specific genital retraction disorder should be reserved for those cases where the cultural factor is clearly delineated. Fourth, the added sociocultural dimension of whether the case occurs in an individual or in the context of an epidemic should be specified to complete the full picture of koro. We believe this manner of classification adheres closely to the philosophy of *DSM-III-R* and represents the most parsimonious way of including a genital retraction disorder in the new manual. This method can also provide a model for examining other culture-specific disorders.

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APPENDIX 1. Proposed Description of Koro in *DSM-IV*

The essential feature of this disorder is a complaint of genital retraction with a fear of impending death, occurring where culturally sanctioned beliefs of folk disease or pathology are present. Among males, the most common complaint is that of the penis shrinking into the abdomen and resultant death; among females, the shrinking of the labia or breasts and resultant death. The person may appear to be in a state of acute distress and attempt to pull his penis, have family members or friends hold onto the penis, or use clamps or string tied to the penis to prevent retraction.

Associated features. The complaint is almost always accompanied by panic, fear, and/or anxiety.

Age at onset. The age at onset is early adulthood to the fourth decade, but all age groups may be affected. Children are rarely affected except in the course of an epidemic.

Course. The disorder is usually self-limiting but may persist for a period of days or weeks. Relapse is possible and may persist for years. Social, occupational, and psychological functioning may be impaired, and marked disruption is common.

Complications. Insomnia is frequently present. The fear of death and the conviction of having a fatal illness may lead to depression and suicidal thoughts. Genitals may be injured by the careless use of clamps or strings.

Prevalence. The disorder is uncommon except in the context of an epidemic. It occurs most frequently among Chinese in South China or Southeast Asia. It has been reported among Thai, Asian Indian, and other Asian groups. Sporadic cases among Chinese immigrants in Western countries have also occurred.

Predisposing factors and sex ratio. The disorder usually affects individuals with low educational attainment. Males outnumber females. Individuals frequently have conflicting feelings about masturbation, sexual identity, and/or sexual intercourse.

Family pattern. No information.

Cultural background. The following sociocultural factors may be present: 1) a belief in folk disease called koro (among Malays), *suk-yeong* (among Cantonese-speaking Chinese), or *suo-yang* (among Mandarin-speaking Chinese), 2) a belief that the excessive loss of semen from too much intercourse may cause involution of the penis, 3) a belief in ghosts of the dead who are capable of stealing penises from the living, 4) a belief in the inducement of genital retraction by the ingestion of contaminated foods, 5) other cultural beliefs.

Differential diagnosis. Delusional disorder, somatic subtype; body dysmorphic disorder; panic disorder; schizophrenia; organic delusional disorder; sexual disorder not otherwise specified.

Book Forum

Nancy C. Andreasen, M.D., Ph.D., Editor

The books for this month are a holiday gift list:
books to broaden the library and the mind,
to provide pleasure and enjoyment,
to give to oneself and others.

HISTORY

The Anatomy of Madness: Essays in the History of Psychiatry, vol. III: The Asylum and Its Psychiatry, *edited by W.F. Bynum, Roy Porter, and Michael Shepherd. New York, Routledge, 1988, 340 pp., $57.50.*

Lectures on the History of Psychiatry: The Squibb Series, *edited by R.M. Murray and T.H. Turner. London, Gaskell (Royal College of Psychiatrists), 1990, 211 pp., £10.00 (paper).*

Of the making of many books there is no end—especially when it comes to writing psychiatric history. Although the modern Ecclesiastes may not find that their "study is a weariness of the flesh," the profusion of papers from modern historians of psychiatry can lead to perplexity and confusion in the reader. The two books noticed here are representative of the genre and reflect a growing interest in the subject that has recently seen the creation of a new journal, *History of Psychiatry,* under the joint editorship of two distinguished scholars, Dr. German C. Berrios of Cambridge University and Dr. Roy S. Porter of the Wellcome Institute for the History of Medicine in London.

Volume three of *The Anatomy of Madness* completes a trio, of which the first two volumes were published in 1985 (1, 2), containing a series of papers read at seminars held at the Wellcome Institute. Encouraged by their warm reception, the editors specially commissioned the essays that make up the third. As its title implies, *Lectures on the History of Psychiatry* contains the annual Squibb lectures, which were delivered at the Maudsley Institute of Psychiatry between 1972 and 1988. Taken together, these volumes form a veritable library of modern historical writing about the development of psychiatry as a discipline and a science, and are a testament to the rich diversity and sophistication of a field of scholarship that has flowered during the past two decades.

It is impossible in the space of a short review to do justice to the 24 separate papers that constitute these two volumes, but taken in the aggregate they provide a composite picture of the paths followed by modern historical research. Since they were sponsored by and delivered at a world-famous medical psychiatric institution (the Maudsley), it is not surprising that half of the Squibb lectures are written by physicians. That this may be a skewed sample is suggested by the fact that only one of the 12 authors included in *The Anatomy of Madness, vol. III,* has a medical degree; indeed, in all three volumes of that trio the proportion is nearly as low, physicians numbering only four of a total of 36 authors.

It is clear from these figures that the history of psychiatry has become a special area of scholarly endeavor in its own right. It is now the preserve of scores of well-trained historians who, though they share a common interest with clinicians in psychiatric phenomena, have become a professional discipline unto themselves. *Pari passu* with that maturing, the writing of psychiatric history has moved from being a mere bald chronicle of events to a concern with the development of psychiatric concepts, theory, practice, and institutions in their relation to the larger social forces that surround them. The wealth of information unearthed by modern historical research from the documents of the past is rapidly accumulating, and if the variety and complexity of detail are at times a bit daunting as it spills pell-mell from learned monographs and papers, one may hope that it may eventually find its way into a new general history of psychiatry that will be more intellectually profound and substantial than any it has hitherto been possible to write. Meanwhile, like paintings in a gallery, there is something for everyone with a curiosity about the history of our discipline in the publications now pouring from the presses, of which the two volumes under consideration here can be recommended as sterling exemplars.

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J.C.N.

BIOGRAPHY

Dream Song: The Life of John Berryman, *by Paul Mariani; edited by Maria Guarnaschelli. New York, William Morrow & Co., 1990, 502 pp., $29.95.*

> We poets in our youth begin in gladness;
> but thereof come in the end despondency and madness.
>
> —Wordsworth, "Resolution and Independence"

When John Berryman was 12, his father shot and killed himself. His wife said he was cleaning his gun. Others believed it was suicide.

John Berryman never doubted it was suicide. For the rest of his life he fought the urge to kill himself. Eventually he did, jumping off a bridge in Minneapolis.

His wife of 14 years, Eileen Simpson, wrote a beautiful memoir about Berryman and his gifted friends (1). She noted that Berryman's father died at 39, John at 58. Poetry, she believed, kept John alive. Suicide was his "subtle foe." As long as he wrote, he refused to be pulled under the current—

literally. When the Muse failed him, he lost any reason for living.

A sad yet heroic story. A brave and talented man fighting heavy odds: shyness, insomnia, hypochondriasis, depression, and serious alcoholism. It is told here, in the first full-scale Berryman biography, in harrowing detail. There is a drone to the march of events: John at prep school, John at Columbia, John on a scholarship to Cambridge. Then a procession of teaching jobs: Harvard, Princeton, Iowa, finally a professorship at Minnesota. One wife, two wives, three. Obsessed with poetry. One thin volume after another. Craving fame, fearing fame. Finally, too late, too old, too beat, achieving fame—the ultimate 15 minutes, his face on the cover of *Life*.

And what was the *Life* story mainly about? Ah, John's drinking. It is unlikely that John would have been on the cover if he had not been a famous drinker.

The mostly nonreading public looks for a charismatic flaw in their mostly unread geniuses, and in the United States, in the twentieth century, the preeminent flaw has been drunkenness. Berryman was a member of a second generation of great American poets of this century, Eliot and Pound having led the first wave. Into the late 1930s they emerged: Blackmur, Jarrell, Schwartz, Lowell, Roethke. They all drank, except Randall Jarrell, who selected his own road to oblivion, walking in front of a car on a dark night. They wrote poems, seduced coeds on speaking tours, got drunk in public and private, became manic, became depressed, died miserably.

Their drinking started rather late in life, as American drinkers go. Berryman was 33 before he started drinking heavily. He had a breakdown and saw a psychoanalyst. He was in and out of hospitals, mainly to dry out. Toward the end, as a patient in a Minneapolis alcohol treatment center, he wrote Eileen, "If we had known I was alcoholic—maybe AA cd have saved me." Eileen wrote,

> No, I hadn't known he was an alcoholic. He had been diagnosed as being a "problem drinker." And I had been convinced that drinking was window dressing—very fancy, very messy, very noisy, very convincing window dressing, camouflage to permit him to hide from the real threat, his subtle foe. (1)

In Mariani's biography, there are many more references to depression, thoughts of death, loneliness, and insomnia than there are to alcoholism. Some believe that there are two types of alcoholism: familial and nonfamilial. The nonfamilial type has a late onset and, some believe, is often associated with affective disorder. Mariani makes no mention of alcoholism in Berryman's family. This combination of late onset and negative family history is common in Berryman's generation of alcoholic poets.

In fact, Nancy Andreasen, editor of this Book Forum, published a study of 30 creative writers in 1987 (2). Eighty percent had affective disorders; 30% were alcoholic. The study had a surprise: only 7% of the writers' relatives were alcoholic. There was a lot of affective disorder and creativity in the writers' first-degree relatives, however, suggesting that these traits run together.

In short, the famous link between alcoholism and creative writing among Americans in this century may be mediated by affective disorder—in some cases. In my own study of drinking writers (3) I found that some were familial (e.g., Faulkner) and some were nonfamilial with a family history of depression (e.g., Hemingway). Mariani's biography suggests that Berryman had frequent bouts of suicidal depression and that alcohol was an anodyne.

When Berryman died he was working on a book called *Recovery* (the first of the recovery books), written as a novel. It was not very good. But his superb *Dream Songs,* written in his 50s, would suggest that his talent survived many years of spectacularly heavy drinking. Some say drinking destroys writing talent, but apparently not always.

Only on that cold day in January 1972, Berryman saw his talent gone forever and did what he felt was the necessary thing.

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Mozart in Vienna: 1781–1791, *by Volkmar Braunbehrens; translated from the German by Timothy Bell. New York, Grove Weidenfeld, 1990, 481 pp., $25.00.*

Innovative biography, if it is to be meaningful, should have a particular focus or philosophy that is unique. The volume under review, a translation from the German, fulfills this criterion. Relying on primary sources, this report "deliberately confines itself to the portrayal of Mozart's external life in Vienna. It seeks to replace careless certainty with new perspectives" (p. 7). These new perspectives bring into center stage cultural, historical, political, and social issues that played important roles in influencing Mozart. "We know he was very interested in what was going on about him and that his Viennese operas contained challenging political themes. He was involved with Freemasonry when this was risky. And he was one of the first independent, self-employed musicians to compose for a musically educated public for *all* social levels" (p. 5).

Many authors have used the romance of Mozart's short but very creative life, perhaps due to the fascinating details. Braunbehrens and others have noted that many of the legends, myths, distortions, gossip, rumor, fantasies, and reconstructions do not reflect actual historical facts. Mozart moved to Vienna in 1781 and died there in 1791. This last decade of his brief life, his period of greatest creativity, is one about which we know relatively little. There are few letters and few verified documents that lend authenticity to the various reconstructions advanced by his later biographers and theorists. Yet, biographers' and historians' reconstructions have value in that they may help in formulating hypotheses that can be tested with data derived from many sources.

What about the impact of what was going on in Western Europe during this last decade of Mozart's life? As Braunbehrens notes, the period of Mozart's residence in Vienna occurred concurrently with the reign of Emperor Joseph II (1780–1790). This "Josephine decade" was a period of enlightened reform through the direct action of the Emperor. Reform was in the air—the curtailing of the influence of the Vatican, the institution of a new taxation system, the abolition of censorship, greater personal freedom, and greater tolerance of minorities. However, in France the Revolution was beginning, and many people wanted a more active role in their political, social, and economic fate. Mozart was very interested in these developments, especially as he observed them in Vienna.

Volkmar Braunbehrens, born in 1941 in Germany, is a well-known music historian, journalist, and author of a biography of Salieri. This book on Mozart is not only a biography of the composer but a history of the "Josephine decade." There is no technical or aesthetic analysis of Mozart's musical compositions.

Psychiatrists are interested in the lives of their patients. It is from these autobiographical accounts that we arrive at diagnostic formulations. The origins of unusual behavior and affects and thought disturbances also come from the self-expressed communications of our patients. In a sense, biography, allied to the case history, is an essential part of our evaluation and consequent therapeutic recommendations. The life of a most gifted, talented creator of superlative musical productions is of special interest to many—not for the purpose of making a diagnosis but of understanding how, when, and from where the roots and directions of genius derive.

This well-written book demonstrates excellent scholarship and, by limiting its focus to the last years of Mozart's life and the external ambience in which he lived and worked, allows the reader to "feel" and participate in a slice of the life of this musical giant. Careful documentation gives the material convincing authenticity. Myths about Mozart's death and burial are examined carefully, and where the evidence disproves the commonly held erroneous conclusions, the author says so clearly. This is skillfully presented in the discussions of Mozart's final illness and his burial. Josephine regulations concerning death and burial, especially as they related to overall public health policies and in order "to eliminate the heavy financial strain of burials among a generally poor population" (p. 414), were the bases of the burial ordinances. The court decree on these matters is fully documented by Braunbehrens. Thus, Mozart did not have a pauper's burial; this legend, as well as others, is refuted, emphasizing what we all seek—accurate evidence to buttress our conclusions. This lesson is taught, perhaps learned, and applied in our clinical work as well as in our understanding of lives that are reported by careful biographers and historians.

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Mozart: The Golden Years, *by H.C. Robbins Landon. New York, Schirmer Books (Macmillan), 1989, 256 pp., $29.95.*

The year 1991 is 200 years after 1791. A simple fact, but to the makers of festivals and the publishers of books it is also 200 years after Mozart's tragically early death. For example, Lincoln Center in New York is planning to perform all of his more than 600 compositions, and *Mozart: The Golden Years* is only one of a number of recent biographies, with, I would guess, more to come. Despite the brouhaha, this surge of publicity and, one hopes, of public interest is welcome.

H.C. Robbins Landon is a distinguished musicologist, most famous for his five-volume *Haydn: Chronicle and Works* (1). In *Mozart: The Golden Years* and in several other works (2, 3), he turns to Haydn's younger friend. One can hope that he is building toward another definitive multivolume work that examines both artist and product.

Meanwhile, we have this important slice of Mozart's life, from age 25 to his death, his 10 years in Vienna. This remarkably productive period, even for this remarkable man, saw six new operas, a mass, a requiem, piano concertos 11 through 27, four horn concertos, six symphonies, 10 string quartets, seven quintets, etc., totaling 158 works—not including dance music and other smaller pieces. It was also the period of his courtship and marriage, his father's death, and a series of important changes in Viennese life.

The author describes his book as an attempt to bridge the gap between specialist and general reader, to explain complicated events and complex music in simple terms. In addition to portions of his life history, we meet Mozart's family and friends (particularly Haydn), patrons, and competitors, and we enter aspects of his world—the concerts and balls and the occasional, difficult travel. Mozart was strongly influenced by the then liberal enlightenment views and was an admirer of Emperor Joseph II's reforms. These included a measure of religious freedom and legal, judicial, and tax reform. One can guess that Mozart's membership in the Masonic Order lodge called "Crowned Hope" was part of an alliance with the forces for social liberalization.

Robbins Landon succeeds to some extent in introducing the musical layman to the elegant abstract structures that underlie Mozart's moving music. It is important for the musically uninitiated to know that in addition to the ineffable aspects of music (in many ways echoing the difficulties we have in describing affects by anything other than the epiphenomena), there is a language and grammar to music understandable to the initiate.

Mozart is of special interest to physicians, and particularly to psychiatrists. He was ill often enough and variously enough to form the basis of a mini-textbook of infectious disease: catarrh and erythema nodosum, rheumatic fever, typhoid, smallpox, a dental abscess, tracheobronchitis, and hepatitis. He almost surely died of renal complications of his repeated streptococcal infections, certainly not from poisoning, Peter Shaffer's *Amadeus* notwithstanding. For his medical information, Robbins Landon relies heavily on Peter J. Davies's *Mozart in Person* (4). Davies, echoed by Robbins Landon, suggests that Mozart was manic-depressive, or at least cyclothymic. Although his depression may have been a combination of normal bereavement and depression secondary to his serious and then terminal illness, the periods of hypomania are well documented. These periods of elation included elevated mood and energy, decreased sleep, joking, punning, and frivolous behavior. However, there appears to have been little if any impact on his creativity and productivity.

Mozart: The Golden Years is perhaps best read along with the author's *Seventeen Ninety-One: Mozart's Last Year* (3), which offers a remarkably intimate glimpse of the composer's death, including a floor plan of the Mozarts' last apartment. The illustrations in both books also help us imagine ourselves in Mozart's world. Although I would choose Davies's book for the medical data, and perhaps Volkmar Braunbehrens's *Mozart in Vienna* (5) for pure biography, Robbins Landon offers a delightful and insightful blend of biography, social history, and musicology. It looks a bit like a coffee-table book, but it deserves to be read cover to cover.

All three of these books are post-Stracheyian demythologizing biographies. However, the removal of the myths and the presentation of a nonidealized Mozart can only increase our admiration and amazement at his achievement.

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Bitter Fame: A Life of Sylvia Plath, *by Anne Stevenson. Boston, Houghton Mifflin, 1989, 386 pp., $19.95.*

The death of an ordinary person usually touches at least a score of lives, while the death of a powerful person may affect the fate of thousands. When the death occurs through assassination or suicide, however, a mythic dimension is often added. Such has been the case with the death of Sylvia Plath. Her suicide on Feb. 11, 1963, is still sending reverberations through the collective imagination and consciousness of her survivors.

This book is heralded as "the first authoritative biography" of Sylvia Plath to date. Previous reconstructions of her life and death have depended heavily on her own autobiographical novel, *The Bell Jar* (1), on a volume of letters written to her mother, *Letters Home* (2), on her poetry, and on other brief accounts of her life such as that contained in *The Savage God* by A. Alvarez (3). This biography of Sylvia Plath is based on written reminiscences and interviews with many of her friends (e.g., Dido Merwin, Richard Murphy, and Lucas Meyers) and some family members (e.g., her sister-in-law Olwyn Hughes).

The details of Sylvia Plath's life are well-known. Her father Otto was a biology professor at Boston University who died of diabetes when she was 10 years old. Her mother, Aurelia Plath, was devoted and self-sacrificing, helping her two children grow into successful, high-achieving adults. While attending Smith College on a scholarship, during her junior year Sylvia suffered a serious depression, which was treated with both somatic therapy and psychotherapy at McLean Hospital. She went on to graduate with honors and subsequently attended Cambridge on a Fulbright Scholarship. While at Cambridge, she met and married Ted Hughes, a distinguished British poet, and subsequently gave birth to two children. On the surface, Sylvia was a bright, affirmative, successful woman who established her own independent career as a poet while simultaneously doing all the other things that women were expected to do in the 1950s and 1960s—cooking, sewing, and tending children. Below the surface, however, there were tensions. Eventually Ted and Sylvia split up. Sylvia became steadily more depressed and ended her life in 1963, leaving behind two young children.

A few days before her death, she described her own suicide in one of her most beautiful poems, "Edge," which begins,

> The woman is perfected. Her dead
> body wears the smile of accomplishment,
> the illusion of a Greek necessity
> flows in the scrolls of her toga.

She goes on to describe her dead children coiled at the feet of the pure white statue that she has become in her imagination. Through her death "she has folded/Them back into her body," just as the petals of a rose fold at night. In this poem, as in many of her best, she was literally exploring life (and death) at the edge. She was quite familiar with the concepts of psychoanalysis and probed her relationships with her father and her husband in "Daddy," which she described in a BBC interview as a portrayal of the Electra complex. Primary process material, controlled and shaped through her poetic imagination, floats very close to the surface of many of her poems.

The interpretation of her life and work has varied. Many of the early descriptions tended to idealize and romanticize her, seeing her as a suffering artist who risked and explored too much. The publication of her letters to her mother, *Letters Home,* portrayed a cheerful, courageous, conscientious Sylvia who brightly stared down adversity and made it slink away.

Anne Stevenson's portrayal looks more closely at the dark side of Sylvia Plath. This book suggests that the tight control she attempted to maintain could not always be achieved in her day-to-day relationships. On many occasions, she was callous, self-centered, selfish, temperamental, demanding, controlling, and even cruel. While the Plath of *Letters Home* wears the guise of a controlled obsessional, the Plath of *Bitter Fame* is a highly intelligent borderline. The book contains a series of fascinating accounts of her selfish, insensitive attitude toward human relationships, whether they were with pen pals (Eddie Cohen), friends (the Merwins), or family (Ted and Olwyn Hughes).

The relationship between creativity and psychopathology is endlessly fascinating. Did Sylvia Plath's character pathology enhance or detract from her creativity? Was she right or wrong to sacrifice human relationships in her single-minded pursuit of artistic success and perfection? These questions are implicit throughout *Bitter Fame,* and readers who ponder the implications of Sylvia Plath's life and work will find themselves perplexed, troubled, but also enlightened after reading this book. For Sylvia Plath and those near to her, the price of fame was a cup brim full of bitterness.

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N.C.A.

Vincent van Gogh: A Psychological Study *(1967), by Humberto Nagera. Madison, Conn., International Universities Press, 1990, 182 pp., $25.00; $19.95 (paper).*

In 1967 Humberto Nagera, using the prevailing theoretical system of the time, published his psychoanalytic study *Vincent van Gogh.* It has been republished this year, the centenary of van Gogh's death. In the quarter century since the book was first published, the art and science of psychiatry have changed, and *Vincent van Gogh* demonstrates why psychoanalytic biographies may well be past their prime.

In 1967 Nagera dismissed the issue of van Gogh's diagnosis by writing that "the question of labelling his illness diagnostically is in itself *irrelevant*" (italics added). To justify this position Nagera argued that diagnostic classifications in psychiatry were insufficient, at times useless, and that they could only loosely link the clinical descriptions or syndromes with the causative, i.e., etiologic. He further set forth the notion that psychiatric concepts of health and illness, difficult to define, were of necessity imprecise, and that we all step from mental health into mental illness and back again. Nagera's thesis was that van Gogh's mental illness resulted from specific psychological stresses that played a pivotal role in triggering his psychotic breakdowns.

There was and still is truth in some of these arguments, but making generalizations from a few specifics is logically dangerous. It may be true that some psychiatric diagnoses are vague, imprecise, and do not yet directly lend themselves to helping patients. Since 1967, however, we have seen the introduction of increasingly systematic and reliable diagnostic systems, as well as a number of potent and relatively specific treatments (including lithium, clomipramine, clozapine, many antidepressants, combinations of psychotherapy and medications, and substantial refinements in the treatments that were available 25 years ago). The effective use of these treatments is predicated on accurate diagnosis and, indeed, one can make a compelling argument that much of the improvement in health care occurring over the last 100 years —in medicine in general and psychiatry in particular—is contingent on the ability to make accurate diagnoses.

There are many reasons, in addition to treatment considerations, why formulating a diagnosis is important. Vincent van Gogh had some form of psychotic illness, most arguably manic-depressive illness (our unpublished data). The scientific evidence for a biological substrate in this disorder is indisputable. For those individuals whose psychotic illnesses are based on a genetic or other primary biological alteration in brain function, retrospective and tortuously convoluted psychodynamic formulations of their thoughts, feelings, and behaviors are often dangerously misleading. Such formulations, while adding a seductively complex aspect to personality, are more likely to be the projections of a theoretical system stretched far beyond its explanatory power than reflections of the truth of an individual life.

Biographies should be firmly based on that which is actually known about an individual, and it is unfortunate that, in addition to everything else, *Vincent van Gogh* was not updated. Twenty-three years after the book was first published, we have some important new facts about van Gogh and his family. For example, although it is well-known that van Gogh's sister, Wilhelmina, spent the last 39 years of her life in an asylum after first showing signs of "insanity" at age 41, there is now evidence that van Gogh's youngest brother, Cornelius, killed himself (1). Another brother, Theo, had severe and recurrent depressions, as well as some form of psychotic illness during the last months of his life. The strong familial history of suicide, psychosis, and depression cannot be ignored in any meaningful attempt to understand van Gogh.

Another fact that has intrigued many of van Gogh's biographers, and one that has provided a remarkable degree of psychodynamic speculation, including much by Nagera, is that van Gogh was born exactly 1 year to the day after the birth of a brother, also named Vincent, who died as a newborn. Nagera states that because of the circumstances of his birth van Gogh had "a conviction of his inadequacy and vulnerability in a world of constant unpredictable dangers." Nagera returns to this theme when he discusses van Gogh's mother as being unappreciative of his gifts, saying that because of this relationship, van Gogh was unable to stand up to what life brought him and gave in to suicide. In fact, it is not clear if Vincent knew that the first Vincent was born on the day of his own birth, nor is it even clear that van Gogh ever knew of the earlier Vincent (1). Infant deaths were not unusual during the last century, and there seems to be little direct evidence that Vincent, or his parents, made much of all of this.

Another example of biographical speculations based on only partially reliable information concerns Nagera's interpretations about van Gogh's romantic relationships with women. At age 20—as an art dealer working in London—Vincent fell in love with Eugenie (Ursula) Loyer, who lived at his boarding house. Nagera writes that being rejected by her "led . . . to a severe regression and a breakdown in his ability to relate to others, in his reality adaptation and in his affective life." A more recent biography (1), however, indicates that although Vincent was rejected romantically, his reaction to the rejection may have been grossly overdramatized by earlier biographers.

This book has probably outlived its usefulness. Newer biographies, such as *Vincent and Theo van Gogh: A Dual Biography* (1), provide more accurate information and do not force facts to fit a theory. If psychoanalysis is going to play an important role during the next century, it cannot avoid the advances in the rest of psychiatry and medicine. Unfortunately, this book makes no attempt to keep pace with advances either in medicine or in biographical research.

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Rickie, *by Frederic Flach. New York, Ballantine Books, 1990, 272 pp., $18.95.*

Rickie is the daughter of the author, a practicing psychiatrist from New York City who has chronicled Rickie's severe mental syndrome from 1966 to 1974, ages 14 to 22. Rickie, now a 37-year-old mother of three, adds to her father's story by interspersing recollections, letters, journal entries, and poems written during the troubled years. Together, they appear to emit a message of hope, an example of triumph over psychosis.

Mainly the book deals with the father's bewilderment and the daughter's travails. At the end, when they document the recovery, Rickie's own voice is not convincing and the father does not detail the processes of change. The reason that the first-person narrative fails to convince is that it has been heavily edited. Rickie sounds essentially the same throughout, grown-up, optimistic, remote. She describes seemingly inexplicable behavior and attributes it to, "I wanted the attention." Both the father and daughter seem intent on normalizing whatever experiential or behavioral evidence for mental illness may have existed. This makes the message of hope a paradoxical one. If mental illness were never present, if the symptoms of 8 years were due mainly to iatrogenesis (one of the implications), then Rickie triumphed over ineffective interventions, therapeutic naiveté, and unconscious cruelty, but did she triumph over illness? The uncertainty of what she was grappling with makes this a problematical book to recommend to patients and families. *Welcome, Silence* by Carol North (1) is better in that respect. There the psychiatrist author describes a struggle with schizophrenia that ended when her illness responded to kidney dialysis. Although the treatment might be controversial, the message of hope in that book is unmistakable.

Rickie also pays tribute to controversial treatments—vision correction and megavitamins. Dr. Flach, in addition, credits the power of prayer. Not mentioned as contributing factors to the turn toward health, but chronologically implicated, are love, marriage, and parenthood. Perhaps these, too, were agents of change. This is not to minimize the presence, at a crucial time, of skilled therapists, renewed optimism, and a persistent family. The nature of the distress that was thus allayed in Rickie remains, however, a mystery.

Whatever the diagnosis, this book is also an angry indictment of the psychiatric "system" that failed a family who thought it had access to the very best talent available. The indictment may or may not be merited. In any event, the author is too close to it to make his case convincingly. The book that brings this particular message heartbreakingly home is the evocative documentary work of a journalist, Susan Sheehan, in *Is There No Place on Earth for Me?* (2).

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A NOVEL

The Things They Carried, *by Tim O'Brien. Boston, Houghton Mifflin, 1990, 273 pp., $19.95.*

Bravery is hard work. The price is perilously high, and in war, the obvious rewards are sometimes only ribbon-thin. So why bother?

Plato considered courage one of the four elements of virtue along with temperance, justice, and wisdom. He knew that wise courage carries such moment that in its presence detracting character flaws are often pardonable. At the core of courage, whether moral or physical, is a sense of obligation, and obligations stem from loves and loyalties. Courage may also be a not so simple reflection of a desire to maintain honor and respect weighed against the fear of shame or cowardice. Bravery then appears to be grounded in abstract ideals.

It is the emotions and abstractions of courage and transitions that most absorb Tim O'Brien in his newest book, *The Things They Carried.* This highly original work is no simple war story. It is an unconventionally conceived novel that weaves back and forth across the domains of fiction and biography. On the title page the book is called a work of fiction, but a reader soon recognizes the author's clever maneuvering of literary devices as he crisscrosses the boundaries of fact and fiction attempting honestly to portray the mind of the Vietnam infantryman.

After graduating from college, Tim O'Brien was drafted and served as a foot soldier in Vietnam during the war's watershed years of 1969–1970. He later pursued graduate studies at Harvard. *The Things They Carried* is O'Brien's third book centered on wartime experiences. His first memoir, *If I Die in a Combat Zone* (1), established O'Brien in the highest echelon of contemporary authors who write about men at war. What followed was *Going After Cacciato* (2), the winner of the prestigious National Book Award in 1979. This novel's dreamlike narration and the seductive possibilities of the plot should find particular appeal among psychiatrists. *Going After Cacciato* unfolds when Cacciato, an infantryman serving in Vietnam, decides, all things considered, that he would much rather be in Paris. He then goes over the hill, quite literally, and begins the 8,600-mile walk. The men of his squad follow in pursuit across the sweep of Asia into Europe.

More than anything else, Tim O'Brien in all his works is a gifted storyteller with stories to tell. Like Chekhov's work, many of his sketches are mere fragments—all middles without beginnings or endings. Some chapters of *The Things They Carried* are a tight two pages reminiscent of poetry, a warrior haiku. Many have previously appeared as award-winning short stories.

The book's structure holds as the storyteller skillfully blends vignettes, slices of life, and sudden moments weighted in emotion into a unified narrative. For readers familiar with the literature that emerged from the Vietnam era, *The Things They Carried* is remindful of Michael Herr's *Dispatches* (3), originally written in 1968, which, critically acclaimed, is the best book written about the Vietnam war.

If there is a translatable flaw in *The Things They Carried,* it is not the author's. Any reader without firsthand experience with the values men share in war may perhaps think O'Brien's stories too far-fetched, too improbable, and some even beyond that. Not that O'Brien speaks of horrors—blood and death are not his fascination; rarely throughout the book is a weapon fired. In *The Things They Carried,* the men carried the responsibility for each other's lives. They carried the common secret of cowardice, their unweighed fears and reputations, the mud and stench of the land, and the age that comes with growing up in an afternoon. His subject is the weight of human emotions and conscience—the things all of us carry throughout our lives.

The author's tone sets his work apart from the overabundance of less well-written war narratives. His voice is visceral. Just listen:

> And in the end, of course, a true war story is never about war. It's about sunlight. It's about the special way that dawn spreads out on a river when you know you must cross the river and march into the mountains and do things you are afraid to do. It's about love and memory.
>
> What stories can do, I guess, is make things present.
>
> I can look at things I never looked at. I can attach faces to grief and love and pity and God. I can be brave. I can make myself feel again.

Hemingway's writings throughout his life were also swayed by war's experience. Courage was serious stuff to Hemingway. He wrote, "Courage is of two kinds: First, physical courage, or courage in presence of danger to the person; and next, moral courage, or courage before responsibility, whether it be before the judgment seat of external authority or of the inner power, the conscience" (4, p.

103). *The Things They Carried* speaks to each of Hemingway's kinds of courage and the enduring burdens courage demands.

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MEDICINE AND SOCIETY

Laughing Death: The Untold Story of Kuru, *by Vincent Zigas, M.D. Clifton, N.J., Humana Press, 1990, 328 pp., $24.50.*

Disgusted by the rise of Nazism in his native Germany, Vincent Zigas packed his medical bag and exiled himself to Papua New Guinea. *Laughing Death* is the good doctor's story of his travails among the natives and the Australian medical administrators, and of his participation in one of the great medical discoveries of our time.

Kuru is a fatal disease that affects mainly women and children of the Fore people, who live in the Highlands of Papua New Guinea. The earliest symptoms are disorders of gait and balance; these spread later to the limbs and trunk. As this instability progresses to completely disable the victim, shock-like tremors affect the muscles of the limbs, trunk, and neck. Uncoordinated, lethargic, tremulous, and dysarthric, kuru patients develop strabismus and emotional lability, although intelligence and memory remain intact. Doomed persons often laugh at their own clumsiness, their inability to get food into their mouths, their stumbling gait and falls. Total incapacity proceeds to coma. In the hours preceding death, the patient's body temperature lowers slightly and head lice can be observed as they abandon the dying body.

The Fore are a martial people, and disputes over women, pigs, and gardens frequently generate enough political enmity to cause armed conflict. Raids and retaliation, often in the form of magic, are a way of life. Death never results from "natural causes" but, rather, is invariably thought to be caused by sorcery. Kuru is the ultimate sorcerer's weapon, and once victims believe themselves to be cursed they have no choice but to die. Even Dr. Zigas first conceptualized kuru as a hysterical disorder in which overly suggestive persons are convinced that they are the victims of a sorcerer and then act out their fatal dramas.

After much soul-searching and astute observation, Dr. Zigas came to believe that a biological lesion causes kuru. He contacted colleagues and participated in research looking for a dietary deficiency or an infectious agent. A visiting anthropologist astounded him by discovering that the Fore cut up and ate small portions of the bodies of kuru victims as prophylaxis against kuru. When Dr. Zigas asked his trusted native friends why they had never told him of this practice, they replied, "You never asked us about it." Unfortunately, the examination of hundreds of samples of body fluids and brain tissue failed to reveal any infection.

Then a peculiar person visited Dr. Zigas: "At first glance he looked like a hippie . . . who had rebelled and run off to the Stone Age world. He wore much-worn shorts, an unbuttoned brownish-plaid shirt revealing a dirty T-shirt, and tattered sneakers . . . . He was just plain shabby. He was a well-built man with a remarkably shaped head, curiously piercing eyes, and ears that stood out from his head. It gave him the surprised, alert air of someone taking in all aspects of new subjects with thirst." The person described was Dr. Carleton Gajdusek, an American medical researcher of extraordinary perseverance.

Laughing Death details the arduous ethnographic, epidemiologic, and laboratory studies that resulted in the discovery of the slow virus that causes kuru and the awarding of the Nobel Prize in Medicine to Dr. Gajdusek in 1977 (1). He discovered that kuru in great part was transmitted to women through cannibalism during mourning rites for victims and to their children by contamination through openings in the skin, mucosal tissues, and the open wounds of jungle sores. The book also records the machinations of medical politics in which quite a few Australian leaders are depicted as downright nasty and hungry for personal glory. It is a terrific read with lots of chilling medical anecdotes, exotic scenery, and fabulous customs (e.g., the customary greeting of the Fore is a standing embrace in which both men and women handle each other's genitals). The author spares no one, not even himself, in lively character profiles. Entire lives are summed up in poignant episodes, and the unhappy existences of many colonial settlers are exposed. The author recounts that while reading sex manuals to escape from boredom, he came across a scribbled note in a book from the town public library: "Have a white husband who is seldom at home. I enjoy being married to him, but at this moment I would prefer to be a black man's strumpet rather than his spouse. Any comments?" Dr. Zigas notes, "There were none, at least from me, since I felt sorry for the frustrated wife."

The author clearly has no stomach for petty bureaucrats and self-centered colleagues, but one wonders about some of his recollections and perceptions. In the foreword, Dr. Gajdusek describes the book as "the most remarkable work in existence of abstract impressionistic ironical parody," in which the author "has taken the liberties of imaginative creative writing and protects his truth with the ambiguities of poetry." Parody? Truth? Poetry? Who's on first? Don't worry. Enjoy this book.

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What Kind of Life: The Limits of Medical Progress, *by Daniel Callahan. New York, Simon & Schuster, 1990, 277 pp., $19.95.*

In this wide-ranging and closely reasoned book, Daniel Callahan takes aim primarily at the seemingly intractable problem of rising health care costs. However, this is not his only aim; along the way, he has much to say about the relationship between individualistic and societal values in U.S. society.

That health care costs appear to be escalating out of control is not in question: 550 billion dollars a year and 11.6% of the gross national product are the current fearsome figures. Efforts to control costs by various kinds of tinkering with the economic mechanisms by which health care is delivered have not been really effective; even a transition to a Canadian or British system would only slow, not staunch, the bleeding. According to Dr. Callahan, the basic problem lies not in defects in health care delivery but in the values underlying the way we think about health and disease. Attempts to define health care in terms of individual needs inevitably fail and will always fail because needs and aspirations become fused; people seek perfect health forever and thus come to believe that happiness can be achieved through medicine. The 1947 WHO definition of health as "a state of complete physical, mental and social well being" is the emblem of these aspirations, justifying such excesses as total parenteral nutrition, dialysis and artificial hearts for ailing old people, efforts to keep alive premature infants who weigh less than 500 g, and universal freedom from neurosis through psychotherapy.

New technologies, technology assessment, and research will not prevent people from getting old and sick; instead, these measures extend the ragged edge of medical possibility by converting acute illnesses to chronic ones. They do not seem to make people more satisfied, and they increase suffering and cost. Unfortunately, death will have its day and will exact its price. Thus, medical success ironically creates its own inevitable failures.

The only solution is a radical restructuring of the values by which we judge health care goals. For Dr. Callahan, the ideal of care for all regardless of economic status rather than the siren call of cure for all the ills that flesh is heir to must become the primary obligation of our society. We must moderate the focus on individual choice and "needs" by making health a part, not the whole, of the common good—a means to other life goals, not its end. Thus, concentration on illusory health care goals may be one of the reasons why we spend only half as much on education as we do on medical expenses. Dr. Callahan acknowledges the immense obstacles in the way of accomplishing such a profound shift, but he offers some blueprints. These involve a much more active role for government up to and including some form of national health insurance. He envisages a system with three levels, the first guaranteeing a minimal level of care and cure for all, the second permitting benefit packages mutually agreed on between individuals and their employers, the third allowing personal income to be used for the pursuit of health beyond the first two levels.

Dr. Callahan faces unflinchingly the somewhat apocalyptic conclusion that "effective cost containment is none other than a form of rationing." Although the pain for doctors would be eased by making rationing judgments on categorical rather than individual grounds, doctors still would have to turn away from their founding creed of undiluted loyalty to the preservation and extension of life. In a chapter that provides a searching analysis of its difficult subject, Dr. Callahan explores this "doctor's dilemma" by examining both active and passive euthanasia. He rejects the former but finds moral justification for the latter and defends the allocation of resources with the resulting setting of limits, even in the knowledge that such measures would cost lives, by distinguishing between killing and allowing to die.

The book closes with a plea for discarding the Promethean and destructive ideal of infinite health progress and calls for much public discussion of these important matters.

Thoroughly documented and skillfully written as the book is, one notes a good deal of repetition, particularly of its major points—the degeneration of health needs to unrealizable aspirations, the necessity for caring rather than curing as the keystone of health care, and the inevitability of health rationing if we are to emerge from our present financial morass. I suspect that the repetitiveness stems at least partly from Dr. Callahan's realization that although his analysis is cogent, his message will be unpopular and unpalatable. I also think that the author might have dealt more systematically with the kind of procedures that will be curtailed under his proposals and the impact that such limitations can be expected to have on overall health costs.

Although I am not sufficiently familiar with the field of health care to dispute the details of his argument, there are clearly great difficulties in the implementation of Dr. Callahan's proposed reforms even if they gain theoretical acceptance. First, he seems to be addressing a rather hypothetical public, one that is outstandingly reasonable and able to be convinced by arguments based on principle rather than self-interest. Are Americans, or indeed any large group of people, really possessed of such Roman virtues that they are willing to sacrifice for the common good their own needs as they perceive them? Dr. Callahan may be underestimating the tenacity of the conviction held by most people that staying alive is qualitatively different from and more important than other goals—individual or societal. Second, a democratic society with an increasingly strong egalitarian bias is unlikely to take willingly to a health care system that allows a man or woman to take advantage of a technological innovation simply because he or she has the money for it. It is hard to conceive of politicians risking such a position on the grounds that the assurance that everyone can rely on care will compensate for the inability of some to receive curative measures available to others.

What Kind of Life is an important book. It deals with issues of vital concern to our society and it does so in a thought-provoking manner. Although not written specifically for psychiatrists, it will certainly be of interest to them as physicians, as citizens, and as potential patients who themselves may have to make some hard choices.

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NEUROLOGICAL TALES

Newton's Madness: Further Tales of Clinical Neurology, *by Harold L. Klawans, M.D. New York, Harper & Row, 1990, 218 pp., $17.95.*

Were the awarding of eponyms still an accepted medical practice, the writing of popular books for the lay public by prominent neurologists might be considered a cardinal manifestation of the Oliver Sacks syndrome. *Newton's Madness* is yet another addition to the genre, lacking, unfortunately, the quality of prose and empathic insights that have made Sacks's works bestsellers. The book consists of more than 20 case history vignettes of individuals suffering from such things as Wilson's disease, stroke, temporal lobe epilepsy, Parkinson's disease, Creutzfeldt-Jakob syndrome, and dystonia. In most of these, the patient presents with puzzling symptoms, mystifying every physician consulted except the author. The most successful parts of the formula involve succinct and clear descriptions of possible pathophysiological mechanisms involved in the individual disorders and suggestions of further articles that might interest a lay reader.

Despite its humanistic proclamations, the book loses no opportunity to split the mind from the body. Psychiatrists on these pages come and go, speaking of the superego and failing to observe a Kayser-Fleischer ring. Noting that neurologists have to learn psychiatry because "it's on the Boards," Dr. Klawans informs an unbelieving patient that she is not crazy but simply has a neurological disease. On a later occasion he quotes his mentor, A.B. Baker, to the effect that a psychiatric history is a waste of time because everybody has psychiatric problems and the question is whether a patient has a neurological problem that can account for his or her behavior. In these pages, angry and demanding patients are tamed with a few blunt words and references to Dostoevski, and patients with dementia are made content with obscure references to a long-forgotten championship baseball team.

The author goes beyond his own clinical practice to apply neurological diagnoses to historical and literary figures. The title chapter puts forth the proposition that Newton's well-known "black year" was really a product of chronic mercury poisoning, the result being paranoia, a move into administration, and a dulling of his former brilliance. There is no evidence, however, that Newton ever experienced dysarthria, tremor, or ataxia. He enjoyed a full head of hair, good teeth, and excellent vision until his death at age 85 and, 4 years after the culmination of his supposed toxicity with heavy metals, was able, in the course of one night and after a hard day's work serving as Warden of the Mint, to solve a problem that had mystified the leading mathematicians of Europe for years. It is this selective rendering of facts that creates doubt about the accuracy of the other situations described and distaste for the rather self-aggrandizing manner in which they are put forth.

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Great Men With Sick Brains and Other Essays, *by Bengt Ljunggren, M.D., Ph.D. Park Ridge, Ill., American Association of Neurological Surgeons, 1990, 130 pp., $45.00; $14.95 (paper).*

Would the German massacre of a huge Anglo-American Arctic convoy have taken place in 1942 were it not for the cerebral glioma that was limiting the function of Sir Dudley Pound, First Sea Lord to Sir Winston Churchill? This is one question from this heterogeneous and highly interesting set of essays by Bengt Ljunggren, a Swedish neurosurgeon and historian. He brings to life historical moments spanning two centuries "from a neurological perspective" through carefully researched accounts, original letters, other primary source material, and a range of photographs and drawings.

There are two main types of focus, the first highlighting the foundations of neurosurgery through glimpses of some of its pioneers and the milestones they achieved. The second involves encounters with eminent persons who developed neurological difficulties as well as the physicians who treated them. There is also one unusual case of a survivor of an embedded nail, with historical antecedents dating back to Biblical times. The accounts branch widely outward from their neurological common points to provide interesting views of the various personalities and their times.

In the 1700s in Stockholm, for instance, we already see attempts to resect visible brain tumors, and we meet Olof af Acrel, the father of Swedish surgery and neurosurgery, whose first attempt followed the insistent pleas of a young man with intolerable headaches. (The patient unfortunately died, as did a great many in those early days.) Some later pioneers include Wilhelm Wagner, the German who trained himself in surgery and innovated an approach to opening the cranial vault; Leonard Gigli from Florence, who invented the cranial saw; Edvard Bull, Norwegian doctor of medicine, who anticipated the carotid ligation for intracranial aneurysms; and his compatriot Vilhelm Magnus, whose later surgical accomplishments included this ligation. Although technical issues are important here, they do not represent the whole and, furthermore, are well within the grasp of the nonspecialist.

It is fascinating when one is able to glimpse the person behind the reputation. Certain accounts allow for this more than others. For instance, the famous American Harvey Cushing, commonly considered to have perfected neurosurgery and introduced it as a specialty at the beginning of this century, was described by Sven Hedin, the explorer of Asia, as "a thin and wiry, distinguished gentleman . . . greeting me gaily and kindly as if we had been acquainted with each other since childhood" (p. 31). Cushing found no evidence of a tumor Hedin feared; the two subsequently became friends, and we are treated to selections from their correspondence, including some touching details of the friendship.

One patient of Harvey Cushing's with a less happy final outcome was General Leonard Wood, and this experience shows us another side of Cushing. He first operated on Wood in 1910, for a meningioma, with success. (Twelve years later, it was Cushing who coined the term "meningioma.") Indeed, one is reminded how far medical technology has come, since the diagnosis was made entirely on a clinical basis. This case represented a turning point in establishing a positive attitude toward brain surgery. Meanwhile, Wood, as we learn in some detail, went on to an active career as a military man and writer, a Republican favorite for President (Warren Harding got the nomination) and Governor of the Philippines, before his condition worsened.

In 1927, Wood returned for surgery; on the operating table, he joked to Cushing about how well he was doing, only to die of unexpected hemorrhage after a large tumor was removed. Cushing was distraught; we witness his reaction, which included rather extreme behavior for a short time. However, we are told that Cushing's overall goal was to keep mortality below 10%. These were difficult days, the pioneers were risk-takers, and the costs were heavy.

We are not to forget that many others helped build our knowledge of the nervous system. In the travels of Axel Key, Rector of the Karolinska Institute, for instance, we briefly visit different European seats of learning in the late nineteenth century. This account features Key's chance meeting with Alfred Nobel, who revealed, among other things, his plans for founding an international prize in medicine. We also see Nobel's work situation and elegant life style at San Remo on the Riviera, yet hear as well of his loneliness, dark melancholic periods, and thoughts of suicide.

Of further interest, perhaps to the psychiatrist in particular, is the essay on Vladimir Bekhterev, the founder of Russian neurology. It is worth merely mentioning a selection of his many enterprises. Bekhterev was a psychiatrist, physiologist, anatomist, teacher, and political activist whose dossier grew ever thicker due to his criticism of Czarist society and Russian educational and other institutions. Bekhterev also provided an effective "counterexpertise" in a Russian version of the Dreyfus affair. All of this makes compelling reading.

In the chapter on Bekhterev, as elsewhere, we see the interconnectedness of major figures in the sciences. For instance, Bekhterev studied in the 1880s with a great many figures (including Meynert and Charcot), was influenced by a visit to Wundt's experimental psychology laboratory, later developed a theory of psychoreflexology, and had a curiously adversarial relationship with Ivan Pavlov. He had a couple of contacts with Freud but was not greatly influenced. His many other accomplishments included description of the reticular formation and work on ankylosing spondylitis. Bekhterev also selected one of the first two "neurological surgeons" in the world and opened the Psychoneurological Institute, the first free university in Russia. Bekhterev's illustrious career was brought to a close after he was called on by Stalin to evaluate his depression and noted Stalin's "grave paranoia." Evidence is marshaled as to the untoward end Bekhterev may then have encountered.

In this case, Bekhterev's own psychiatric history is also of note. At age 17, he was hospitalized for "melancholia," which is cited as a basis for his later professional interests but is not evaluated further. Bekhterev, however, comments on Dostoevsky, whose work some authors had questioned because of Dostoevsky's epilepsy. According to Bekhterev, these works make it clear that "health and disease of the soul are so tightly interwoven in real life that it sometimes seems impossible to distinguish the one from the other" (p. 56). Effects of epilepsy on one's work are not followed up in the later case of George Gershwin, whose great enjoyment of life and remarkable career were cut short at age 38 by a malignant right temporal lobe tumor and who, in retrospect, had shown symptoms consistent with temporal lobe epilepsy for many years.

This book, although frequently fascinating, could benefit, in my opinion, from additional unifying themes and conclusions beyond the evident progress of neurosurgery and its relation to courageous innovators. The chapters and, sometimes, the vignettes within chapters vary in focus and depth of treatment and in the balance of technical versus human interest material, whether centered on neurosurgical advances or the examination of lives.

The question of whether the "greatness" of subjects relates in some negative or positive way to the "sickness" of their brains—which the book's title appears to pose—is not always answered. Nor are the varying answers that are given reconciled with each other. This would have been most interesting to attempt. For instance, it is suggested that sickness interfered with function for figures such as Dudley Pound, but General Wood, on the other hand, is said to have carried out his duties virtually to the end. As for Sven Hedin, the explorer, whose autopsy showed a pituitary tumor, the author humorously speculates that a decrease in pituitary function in his younger years might help explain Hedin's devotion to exploration rather than to the opposite sex.

Little speculation occurs regarding such psychiatric conditions as Bekhterev's or Alfred Nobel's "melancholia." I find such descriptions of particular interest because of our own work (1, 2) and other accumulating evidence for enhanced creativity among persons with affective disorders—particularly bipolar disorders—and their immediate relatives. As indicated, implications of a seizure disorder in Gershwin or Dostoevsky are not addressed, at least beyond Bekhterev's own interesting comment. If one does not somehow complete the great men-sick minds equation, then the choice of eminent subjects for the case histories becomes less compelling.

These last comments are not to distract from the many fascinating and highly entertaining aspects of this unusual book of essays, which is the first title to be published through the Publications Committee of the American Association of Neurological Surgeons. The book is also nicely written and attractively printed and illustrated, and each section includes a range of valuable references. Readers interested in medicine and history, and those who want to see the world through neurological eyes, might have trouble putting it down.

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ON SEX AND ART

Sexuality: An Illustrated History, *by Sander L. Gilman, Ph.D. New York, John Wiley & Sons, 1989, 367 pp., $49.95.*

We've all seen any number of books with this or similar titles in most every remainder catalog that crosses our desks and dismissed them with hardly a thought as dressed-up pornography. This version, however, which might better be titled a "History of Sexual Illustration," is a legitimate and substantial study of semiotics and is distinctly not of the cryptoerotic coffee-table variety. Professor Gilman is interested in how our sense of sexuality has been influenced by the manner in which the prevailing cultures of successive ages through Western history depicted sexual organs, diseases, and acts. Following Plato and Kant, Gilman would have us understand that what we perceive, in this case the human body in its sexual functions, is not the object itself but the object filtered through the limitations of our senses, our cultural presuppositions, and our personal intellectual and emotional functions. He believes that sexuality cannot exist as neutral, objectively observed reality but is available to observation only through the cultural meanings that are inextricably bound to it. In this construct, the semiotics of sexuality becomes sexuality as we perceive it not only intellectually but experientially. Sexuality is an elemental force that enters discourse through conceptual representation, a system of symbolization that "violates its very nature by giving it form and structure." The process of symbolizing this elemental force occurs in words and pictures, and this volume concentrates on how those pictures have been used throughout history.

As might be expected, the volume is copiously illustrated (328 plates, all in black and white) with "objects taken from 'high' art, the art of collectors and museums; 'low' (i.e., mass as well as popular) art, the art of the streets, from advertising to pornography; and, centrally, medical illustration, specifically the history of the anatomical illustration of the genitalia." The art of the museum represents itself as of aesthetic value, the art of the street as of erotic value, and the art of the medical illustrator as of value-neutral education. Medical illustration, which is Professor Gilman's central interest, is typically perceived as the real anatomy, as opposed to the pornographic, aesthetic, or erotic rendering of the same body parts. How these icons are manipulated to enforce moral dogma, particularly in the depiction of sexually related disease, is the moral of Professor Gilman's story. Sexual myth making exists in every age and in every genre of sexual iconography, whether in frankly titillating pornography, fashion models in poses not elsewhere seen in nature, or anatomic illustrations describing organ systems in neatly delineated four-color graphics. Dr. Gilman would have us understand that none of these versions represents "the realities of sexuality, but our fantasies about the sexuality of the dominant discourse."

There is a good deal of psychoanalytic influence in Dr. Gilman's work. His frontispiece is a student's caricature of the author declaiming "Freud's theory of bisexuality," and he is intensely interested in physiological disease and the unconscious and in the role of symbolization as a psychic defense against apprehension of the emotionally intolerable. He finds in gender the repository of all duality, most particularly health and disease, racial distinction, self and other. He sees sexual disease as the icon of sexuality and sexuality as the icon of all existence. Icons, the illustrations that constitute the subject of this book, are seen as "visual boundaries for the idea, or fear, of disease, and boundary as another means of creating the order that we desperately need to understand the world and our place in it." Some of these constructs are harder to take than others. My experience as a psychiatrist has been that sick patients are desperate to recover and feel well again; desperation to understand the world and the relationship of one's disease to it is more likely the exclusive emotion of the philosopher. From time to time I found that such extravagant use of language in this book tended, finally, to trivialize a condition by overstating it; more often it tended toward obscurity.

This is, on balance, a work of considerable thought and scholarship. The collection of plates depicting the history of sexual illustration and sexual mythology from Biblical to modern times is itself a notable tour de force. Dr. Gilman uses the image of sex and the imaging of sex to explore the relationship of our minds to our bodies and of our minds and bodies to the forces of mutability, most prominently represented by the process of disease. These are concepts that one may or may not fully endorse, but the reader will undoubtedly find himself intellectually activated as he remonstrates with Professor Gilman's rich series of associations.

Despite my general appreciation, there are flaws here that struck me as especially peculiar and annoying. The first of these was that the book literally fell apart in my hands after two readings, and I am shuffling unbound pages as I prepare this review. An expenditure of $49.95 will be sufficient to test the buyer's equanimity as the volume disintegrates. A book of this size, weight, and paper quality should be bound in signatures, and the experienced publisher, John Wiley & Sons, should know it. Near the center of the book, intellectually as well as topographically, is a challenging chapter on Goethe and his literary manipulations of sight and touch. Gilman finds in the process of iconography an emotionally secure distancing from what he sees as our "lowest" sense, touch, and our "highest," the sense of sight, and quotes a famous line from "The Roman Elegies" ("*Sehe mit Fühlendem Aug', fühle mit sehender Hand*") to support a central conceit of the book. Disappointingly, the author mistranslates the German, despite his apparent fluency, and confuses a crucial thought. Plate 250, identified as a nineteenth-century engraving of a dissected penis, is, in fact, the drawing of an elbow.

This book will not assist a psychiatrist in the care of patients, and it is not intended, I believe, to train young physicians in the theoretical bases of our profession. It is, however, legitimate intellectual nourishment for those who need no other justification for their reading.

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Pictures at an Exhibition: Selected Essays on Art and Art Therapy, *edited by Andrea Gilroy and Tessa Dalley. New York, Routledge, 1989, 229 pp., $47.50; $16.95 (paper).*

This book contains 19 diverse essays on the relationship between art and psychology and two brief sections of commentary by the editors. The essays are derived from papers presented at the conference "An International Review of the Arts in Therapy" held at the University of London, Goldsmiths' College, in September 1985, sponsored by the British Association of Art Therapists and the International Society for the Study of Art and Psychopathology. Although the conference attracted delegates from all over the world, only the papers of the British delegates are included in this volume.

Part one addresses how theories of psychoanalysis can aid in understanding the imagery of individual artists, writers, and cultures. Part two presents the theory and practice of art therapy, predominantly through casework-based papers. In its entirety, then, the book focuses on the two main areas of concern for art therapists: the art product as diagnostically indicative of an individual's mental state and the process of making art as a naturally therapeutic activity. Although the papers are uneven in quality, overall the book succeeds in showing how psychological analysis can be useful in both areas.

The book begins with an essay by Peter Fuller on the similarity between D.W. Winnicott's theory of the mother-infant relationship and Henry Moore's sculptures of mothers and children. Fuller argues convincingly that both Winnicott (verbally) and Moore (visually) have described the mother-child relationship as it evolves from the original merger that infants experience with their mothers. He also shows how Winnicott's concept of transitional objects, which provide a bridge between the infant's subjective world of imagination and the objective world of outer reality, finds a tangible expression in Moore's art.

Joan Woddis's paper on the verse and illustrations of Edward Lear is also particularly effective. She gives a report of Lear's history, including his abandonment as a youngster by his mother and his repressed homosexual feelings, before building her argument, which concerns how Lear's fears, conflicts, and wishes are reflected in his work. In this way, Woddis does not force Lear into the mold of a general theory, and her conclusions appear to be substantiated. She asserts that Lear's nonsense verse and drawings served as a defense against his childhood pain and as a means to create a compensatory fantasy world. At the same time, his tragicomic verse concerning rejection and loss as well as the isolation of social outcasts allowed him to express and work through his rage and sorrow.

Another engaging article in part one is that of Michael Edwards, who places conflicting theories about the use of art therapy in historical perspective. Edwards posits that the roots of the diagnostic attitude toward imagery—the emphasis on the finished product—lie in eighteenth-century neoclassicism. On the other hand, the roots of the positive conception of imagination and the belief in the natural healing capabilities of art—the emphasis on the process of making art—lie in nineteenth-century Romanticism.

The case studies presented in the last three chapters of part two give poignant examples of what the field of art therapy is all about. Using a family systems approach, Michael Donnelly describes how he helped a boy and his parents, through their drawn images, to realize their communication difficulties and dysfunctional hierarchical structure. Paola Luzzatto, in a beautifully written report, shows how she worked with patients with drinking problems on issues of withdrawal and clinging. For one man, an image of a yellow wall represented his fear of connection with others and the inevitable engulfment. By experimenting with painting adjacent patches of color, omitting the yellow barrier between them, the patient came to a firmer sense of his own identity and a lessened fear of intimacy. Another patient used the yin-yang symbol in working through his symbiotic relationships with his mother and with his wife. And Muriel Greenway explains how she worked with a 9-year-old boy's images of "angry houses" and twin sailboats to help him and his family confront their grief over the boy's lost twin brother.

As noted by Anthony Storr in his brief but engaging foreword to this book, the reader is frequently reminded of the altered transference-countertransference situation in art therapy, where the therapist often sits beside the patient to create or discuss imagery, eliminating the distance that may exist between therapist and patient in many other forms of treatment. It would have been interesting to have a chapter dealing more exclusively with how dream imagery is used in art therapy, since this is the material that Jung—credited in this volume as the founding father of art therapy—frequently encouraged his patients to express visually.

Another dimension of the interpretation of imagery is presented in Roger Cardinal's paper on finding meaning in prehistoric rock drawings through the use of anthropology and semiotics. Although the images of primitive people may visually suggest a tangible referent, Cardinal notes that they usually also hold symbolic meaning relating to themes such as hunting, warfare, sexuality, death, and religion. Inviting the reader to compare these schemata to the images of twentieth-century artists whose work shares primitivistic qualities (e.g., Jean Dubuffet, Joan Miro, and Henri Michaux), Cardinal quotes Miro in reminding us that, "it is signs that have no exact meaning that provoke the sense of magic."

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Reprints of Book Forum reviews are not available.

Letters to the Editor

Neuroleptic Malignant Syndrome Associated With Withdrawal From Carbamazepine

SIR: Neuroleptic malignant syndrome has been reported in patients taking loxapine (1) and when amantadine has been withdrawn from patients taking neuroleptics (2). A case has also been reported in a patient taking clozapine and carbamazepine (3). I recently encountered neuroleptic malignant syndrome in a patient taking loxapine following withdrawal of carbamazepine.

Mr. A, a 40-year-old Caucasian war veteran in good health, had been treated for posttraumatic stress disorder. At his last hospitalization he had presented in an agitated state with paranoid delusions. A diagnosis of atypical psychosis was made, and treatment was begun with loxapine, 250 mg/day, hydroxyzine, 100 mg h.s., and carbamazepine, 200 mg t.i.d. In outpatient treatment his carbamazepine was increased to 1000 mg/day, hydroxyzine was discontinued, and imipramine, 150 mg h.s., was added.

Subsequent examination showed no overt psychosis. Examination for movement disorders showed a very slight rest tremor in the right hand and occasional choreic movements in the face. No rigidity was present. Due to lack of clear indications, carbamazepine was tapered over a 4-week period by decreasing the daily dose by 200 mg each week. At the end of this taper the patient complained of insomnia. Lorazepam, 2 mg h.s., was prescribed. Mr. A's sleep improved. Eleven days after discontinuation of carbamazepine, examination showed him to have some mild cogwheel rigidity, but he was otherwise normal.

On the twelfth day after withdrawal of carbamazepine, Mr. A became increasingly unresponsive. That afternoon his vital signs were temperature, 99.9 °F; pulse, 108 bpm; and blood pressure, 190/110 mm Hg. His skin was pale and he was grossly diaphoretic. He had marked muscle rigidity and a parkinsonian gait. Results of a physical examination were otherwise unremarkable. Mr. A's WBC was 12,600 mm^3 with 79% segmented neutrophils, 14% lymphocytes, and 6% metamyelocytes. His chest X-ray and ECG were normal. His serum creatine phosphokinase level was 983 mU/ml. A provisional diagnosis of early neuroleptic malignant syndrome was made. Loxapine was discontinued and benztropine, 2 mg b.i.d., was added.

The next day Mr. A was more responsive, with reduced rigidity. His blood pressure and pulse had normalized, but his temperature had increased to 100.8 °F. He continued to do well over the next 2 days, with gradual resolution of his confusion, rigidity, and fever.

Although neuroleptic malignant syndrome may occur at any time in the course of neuroleptic therapy, in this case there was no precipitating illness or change in medication other than withdrawal of carbamazepine, except for the addition of lorazepam. Lorazepam is unlikely to have caused the syndrome, as benzodiazepines have been used to treat mild cases (4). Carbamazepine is known to reduce haloperidol serum levels by as much as 50% (5). Although carbamazepine's effect on loxapine serum levels is unknown, it is possible that discontinuation of carbamazepine resulted in increased loxapine blood levels, precipitating the neuroleptic malignant syndrome. The time course of the development of the syndrome is consistent with this speculation.

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Possible Synergistic Anticonvulsant Effect of Propranolol and Carbamazepine

SIR: In animal models, propranolol has been shown to have an anticonvulsant effect that is synergistic with that of carbamazepine (1). This is thought to be due to propranolol's membrane-stabilizing, local anesthetic properties rather than its β-receptor-blocking potency (2). To our knowledge, there have been no reports of an anticonvulsant effect of propranolol in human beings. We wish to report the possible synergism of propranolol and carbamazepine in preventing complex partial seizures in a young woman with an organic brain syndrome following head trauma.

Ms. A was a 21-year-old college student whose head had been repeatedly beaten against a car during a criminal attack; she had lost consciousness for at least 10 minutes. Results of a neurological examination at the time of the injury were unremarkable, but over the next several months, the patient developed a number of neurological and psychiatric symptoms. Clinicians and family members witnessed occasional grand mal seizures as well as more frequent complex partial seizures of two distinct varieties: unresponsive periods with fixed lateral gaze and episodes of horrible screaming and a terrified appearance that lasted several minutes, followed by a longer period of decreased responsiveness and no memory of the outburst when fully oriented (3, 4). Ms. A became quite affectively labile and had unprovoked violent outbursts; during one

> of these episodes she stabbed her boyfriend with scissors. She was frequently hypersexual and was also noted to have disorganized and delusional thinking.
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> An initial EEG when she was not taking medication was normal, and three subsequent EEGs when she was taking medication were notable primarily for generalized slowing. CT and magnetic resonance imaging revealed minimal asymmetry of temporal horn size, the right being greater than the left, but both scans were otherwise unremarkable. Neuropsychological testing was performed on three separate occasions over a 5-year period and each time revealed diffuse cerebral dysfunction.
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> Over the course of several prolonged hospitalizations, Ms. A's condition was stabilized with a combination of fluphenazine, 5 mg b.i.d.; benztropine, 1 mg b.i.d.; lithium carbonate, 600 mg b.i.d.; carbamazepine, 400 mg b.i.d.; and propranolol, 120 mg b.i.d. Carbamazepine levels were in the range of 5–8 μg/ml, and the patient was without clinical seizures or violent episodes for 8 months.
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> However, because of her hypercholesterolemia, an attempt was made to taper Ms. A's dose of propranolol. This was done over a 2-week period without evidence of rebound hypertension while she was in the hospital. Coincident with discontinuation of propranolol, she again began to manifest at least daily complex partial seizures. An EEG done during this period revealed only generalized slowing. The seizures persisted despite an increase in her carbamazepine level to between 10 and 14 μg/ml, achieved by increasing the dose to 600 mg t.i.d. She was restarted on propranolol, 120 mg b.i.d., and her condition stabilized again over the course of 3 days. She has remained seizure free over the subsequent month and has been able to resume taking carbamazepine twice a day.

We believe that in this patient, the combination of propranolol and carbamazepine may have produced a synergistic anticonvulsant effect. While it is possible that these medications did not exert their effects on seizure activity, our clinical observations suggest that they did. This may be of relevance to the treatment of some patients with posttraumatic organic brain syndromes or refractory seizure disorders (5).

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Phenobarbital as an Adjunct for Alprazolam Withdrawal

SIR: Benzodiazepine withdrawal symptoms have been well documented. Noyes et al. (1) reviewed discontinuation studies of persons receiving short- or long-term benzodiazepine therapy. Withdrawal symptoms were noted in six of nine short-term studies and in seven of nine long-term studies.

Alprazolam withdrawal can be problematic. A multicenter trial of alprazolam for panic disorder and agoraphobia (2) described withdrawal symptoms in 35% of the subjects. Tapering the dose of alprazolam may take up to 8 weeks (2). Clonazepam (3) and clonidine (4) have been used to provide a safer withdrawal regimen.

Phenobarbital is cross-tolerant with ethyl alcohol and the sedative hypnotic agents (5). We report two cases of successful alprazolam withdrawal with the use of phenobarbital.

> Ms. A, a 51-year-old woman, had a 3-year history of migraine-like headaches attributed to the onset of fibromyositis and had been treated for 3 years with alprazolam, 13 mg/day, and doxepin, 100 mg at bedtime. She was hospitalized for alprazolam withdrawal. She was placed on a regimen of alprazolam, 11 mg/day, on hospital day 2, along with phenobarbital, 120 mg/day. The alprazolam was tapered by means of a 2-mg decrease every third day; the last dose was given on hospital day 24. She was prescribed phenobarbital, 90 mg/day for days 2 through 25, 60 mg/day for days 26 and 27, and 30 mg/day for days 28 and 29. Doxepin, 100 mg, was continued throughout the hospital stay. Her vital signs remained stable, and she exhibited no signs or symptoms of withdrawal. She was discharged from the hospital on day 30.
>
> Ms. B, a 33-year-old woman, had a 1-year history of back pain. She was prescribed alprazolam and a combination of propoxyphene, 100 mg, and acetaminophen, 650 mg. She gradually increased the alprazolam to 15–20 mg/day and the propoxyphene-acetaminophen to 20–30 tablets/day. She was hospitalized for supervised withdrawal, as she was abusing her prescription drugs. Opioid withdrawal was treated with clonidine, 0.1 mg on hospital day 1, 0.2 mg on day 2, 0.3 mg on day 3, and 0.2 mg on day 4. Alprazolam was tapered as follows: 8 mg on day 1, 12 mg on days 2 and 3, 9 mg on days 5 through 10, 7.5 mg on days 11 through 13, 4.5 mg on days 14 through 16, 3 mg on days 17 through 19, 1.5 mg on days 20 through 22, 1 mg on day 23, and 0.5 mg on day 24. The phenobarbital regimen was 120 mg on days 1 through 19, an increase to 180 mg on days 20 through 22 due to the patient's report of mild withdrawal symptoms, and 90 mg on days 23 and 24. She left the hospital on the 25th day because her husband was arrested and she needed to go home to care for her children.

Both patients had been started on alprazolam for legitimate medical illnesses. Alprazolam was increased for the first patient by her physician in an attempt to control her headaches. Alprazolam withdrawal was accomplished in 30 days with the use of phenobarbital. The patient had an uneventful hospital course.

The second patient increased her doses of alprazolam and propoxyphene-acetaminophen. When she developed withdrawal symptoms on day 20, an increase in the phenobarbital dose led to relief of her symptoms.

Psychiatrists will need to develop and implement strategies to detoxify patients from psychoactive substances in a safe, timely manner. Phenobarbital appears to have promise in dealing with the complex problem of alprazolam withdrawal.

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Survivable Fluvoxamine Overdose

SIR: Fluvoxamine is a compound in the series of 2-aminoethyloximethers of aralkylketones that inhibits neuronal reuptake of serotonin without noradrenergic, monoamine oxidase, amphetamine, or anticholinergic effect. Metabolism is by oxidation of the methoxyl group. The mean plasma half-life is 15 hours after a single dose in healthy volunteers (1). Fluvoxamine is structurally similar to fluoxetine, another serotonergic antidepressant. Neither agent causes arrhythmias, the usual cause of death after tricyclic overdose.

In patients taking this drug, no clinically important changes in heart rate or blood pressure have been observed. Nausea, constipation, and somnolence are the usual symptoms that emerge. The drug is currently marketed in several European countries and is under clinical investigation in the United States.

Two cases of massive overdose of fluvoxamine alone (4.8 g and 3.0 g) have been reported (unpublished); both patients fully recovered. There were no abnormal laboratory or ECG findings in these cases (1). A third patient ingested 5.0 g of fluvoxamine plus bromazepam, Imodium, and whiskey. She had convulsions and recovered. Another elderly woman ingested 3.0 g of fluvoxamine, 60 oxazepam tablets, and 30 temazepam tablets, which resulted in CNS but not cardiovascular death (1). I would like to report a case of my own in which a patient took an overdose of fluvoxamine.

> Ms. A, a 31-year-old woman with cyclic hypomania and depression (bipolar II), began a blind trial of placebo, desipramine, or fluvoxamine. During placebo washout, irritability, agitation, and insomnia were noted, but the study medication was increased to 150 mg/day, with timely remission of depressive symptoms. Six months later, this patient impulsively took 4.8 g of fluvoxamine, 0.75 g of amitriptyline, and 7 g of naproxen. Lavage 1 hour later produced return of pill fragments. She was monitored in an intensive care unit and showed no evidence of arrhythmia. She was dystaxic and somnolent, but she never lost consciousness and she noted marked anticholinergic symptoms from the amitriptyline. She suffered a ruptured cecal diverticulum and required a hemicolectomy.
>
> Fluvoxamine was stopped. One month after the overdose, Ms. A exhibited fast speech, mild euphoria, extreme insomnia, increased energy, marked mood lability, pressure of speech, and hypergraphia. This episode was much more severe than her hypomanic episodes before fluvoxamine use. Administration of lithium carbonate led to euthymic mood in a few weeks.

Fluvoxamine may be capable of precipitating mania, as is the analogue fluoxetine (2–4). Perse et al. (5) reported mania in a woman with obsessive-compulsive disorder and bipolar affective disorder who was treated with fluvoxamine. Investigators should be aware of the potential switch effect of this drug, which, like fluoxetine, appears nonlethal in massive overdose.

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Bupropion and Delirium

SIR: Bupropion, an antidepressant with a favorable side effect profile, has recently become available. Psychosis has been associated with bupropion (1), particularly at doses greater than 450 mg/day. The psychosis is most likely due to the drug's dopamine-reuptake-blocking activity, and caution is advised when using L-dopa with bupropion (*Physicians' Desk Reference*). We report the appearance of acute delirium associated with concurrent use of bupropion and amantadine.

> Mr. A, a 75-year-old man with moderate idiopathic parkinsonism (for which he was treated with amantadine), developed depressive symptoms and paranoid ideation 18 months before hospitalization. His paranoia was refractory to haloperidol, and he could not tolerate tricyclic antidepressants. Daily function was good despite these problems until 6 months before hospitalization, when his condition worsened, prompting admission.
>
> On admission, Mr. A complained of depressed mood and displayed vegetative symptoms, psychomotor retardation, and nihilistic delusions. Results of a physical examination were unremarkable; neurological examination showed significant rigidity, festinating gait, and resting tremor. Findings of a laboratory evaluation were normal. ECT was initiated after a pretreatment work-up revealed no contraindications. Seven biweekly unilateral (nondominant) ECTs resulted in marked improvement of the depressive and parkinsonian symptoms; no significant confusion or memory changes were noted. After ECT, bupropion, 75 mg b.i.d., was added; other medications

(haloperidol, 2 mg/day; amantadine, 300 mg/day; benztropine, 2 mg/day) remained unchanged. After a cumulative bupropion dose of 450 mg over 72 hours, Mr. A became disoriented and agitated, with visual and auditory hallucinations, impaired attention and memory, and a fluctuating level of awareness. His gait was unsteady, resulting in a fall. Bupropion was discontinued, but the other medications were unchanged. Neurological examination revealed impaired cerebellar function, including dysdiadochokinesia, dysmetria, and positive Romberg's sign. An EEG demonstrated only diffuse bilateral slow wave activity. Laboratory measures and a head CT scan were unremarkable. The patient's delirium resolved over the next 4 days.

Agitation, disorientation, impaired attention, hallucinations, and acute loss of cerebellar function with EEG changes indicative of encephalopathy clearly define delirium. These symptoms began with the initiation of bupropion and resolved when it was discontinued. Cerebellar dysfunction has been associated with bupropion (according to the package insert), but there have been no reports of delirium. One explanation for the delirium is synergism between bupropion and amantadine. Bupropion inhibits dopamine reuptake; amantadine facilitates release of presynaptic dopamine. Together they may cause dopaminergic overdrive (despite the use of a competitive inhibitor such as haloperidol), with subsequent delirium. In addition, anticholinergic agents (e.g., benztropine) may further enhance dopaminergic transmission or cause delirium on their own. Last, pharmacokinetic interactions between bupropion and amantadine or benztropine could have produced elevated serum levels of these agents, resulting in delirium.

Bupropion's favorable side effect profile makes it appealing in treating elderly depressed individuals. However, this same population also frequently suffers from parkinsonism and is often treated with dopaminergic agents; their combination with bupropion may result in delirium. We suggest caution in the concurrent use of bupropion and dopamine agonists, even at the lowest doses.

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Therapeutic Drug Monitoring of Bupropion

SIR: Therapeutic drug monitoring is an accepted tool in practice and is readily available from commercial laboratories. Given its availability and its usefulness for some classes of antidepressants, there is a tendency to rely on therapeutic drug monitoring for new antidepressants before it has been adequately tested. Such is the case with bupropion, first of a new class (aminoketones).

There have been three studies relating plasma concentrations of bupropion alone (one with 61 subjects [1] and one with 15 subjects [Preskorn et al., unpublished]) or with its metabolites (10 subjects [2]) to its antidepressant effects; however, they have limitations. In the first two studies, maximum response was observed at trough bupropion concentrations under 100 ng/ml. A similar trend was observed by Golden et al. (2), but it did not reach statistical significance, perhaps because of the small sample size. The latter study did report that high plasma levels of the metabolites, particularly hydroxybupropion, were associated with less antidepressant response. Still, reliance on therapeutic drug monitoring to guide bupropion dose adjustment is premature and potentially dangerous for the following reasons.

Bupropion is extensively metabolized to pharmacologically active metabolites. As reflected by changes in plasma concentration, the half-life (time required to eliminate one-half of the amount of drug in the body) of bupropion has two components: an alpha (disposition) half-life of 1½ hours and a beta (elimination) half-life of 4–24 hours (3). In contrast, half-lives for the metabolites can be as long as 43 hours. While bupropion plasma concentration may be high 1–4 hours after a dose, it can fall by 75% over the next 4 hours. In contrast, metabolites reach concentrations more than 10 times that of bupropion and remain high over the entire dosing interval. After a dose adjustment, bupropion will achieve steady state in 3–5 days, while metabolites may take 10 days.

These facts raise the question of when plasma should be sampled in relation to duration of therapy and time of dose, since the relative contributions of bupropion and its metabolites to efficacy and safety are unknown. For seizure, the principal safety concern with bupropion, there is a correlation with bupropion dose, but there are insufficient data to correlate seizure risk with bupropion or metabolite plasma levels (4).

Furthermore, reliable assays for bupropion and its metabolites exist, but they are complicated. Results may vary depending on the capability of the laboratory employed. Also, bupropion is unstable in plasma (5). More experience is needed in transferring these assays from the experimental to the reference laboratory.

The goal of therapeutic drug monitoring is to improve efficacy and reduce toxicity. Given the paucity of information, reliance on monitoring of bupropion to accomplish this goal is not feasible. We are concerned that use of therapeutic drug monitoring for bupropion might lead clinicians to adjust the dose inappropriately or even raise the dose above 450 mg/day, which is not recommended. Until definitive information is available, the value of therapeutic drug monitoring for bupropion in practice is limited (perhaps, it should be used solely as a compliance check) and must be cautiously employed.

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Concept of Psychological Trauma

SIR: We believe that the following, on the origin of the concept of psychological trauma, may be of interest to the readers of the *Journal.*

The concept of psychological trauma has taxed the best psychiatric minds since the late nineteenth century. It is widely believed to have originated with Breuer and Freud (1), but as with the concept of the unconscious, psychological trauma had earlier antecedents. We feel it is worth mentioning them because of their continuing relevance for the nosology of posttraumatic stress disorder.

The nineteenth-century French psychiatrist Janet (2) saw psychic trauma as crucially mediated by vivid or "vehement" emotions. These were further prompted by traumatic memories and exerted a disintegrating effect on the mind (3). The first to introduce the term "psychic trauma," however, was the German neurologist Albert Eulenburg in 1878 (4, p. 589). He believed that "psychic shock," in the form of sudden vehement emotions such as terror or anger, could better be called psychic trauma. He regarded this "sudden action of vehement emotions" as an actual molecular concussion of the brain, which he likened to the *commotio cerebri* postulated in physical trauma. Since then, other German physicians have also equated the concepts of psychic shock and psychic trauma (5). It is only recently, however, that these ideas regarding the molecular basis of posttraumatic stress disorders have begun to find a basis in scientific fact rather than fancy, as exemplified in research on trauma and neurotransmitters.

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Limitations of Fluoxetine

SIR: I wish to report an increasingly common but underappreciated phenomenon seen with the antidepressant fluoxetine. This phenomenon typically appears in patients who have recently heard about fluoxetine from a television talk show, from the lay press, as in the recent cover story in *Newsweek* (1), or from a friend who heard about the medication from one of these two sources. Typically, the patient has a long history of dysphoria and interpersonal difficulties and has several psychosocial stressors. The patient comes to the clinic and asks for "Prozac" by name. There is an expectation, spread about by the sources I have named, that fluoxetine is a wonder drug, devoid of side effects, which will make one into a new person. Curiously, when fluoxetine is indicated and prescribed, after it begins to exert its therapeutic effects, many patients realize that the medication will not change the problems in their lives. They realize, for example, that they will need to find jobs, that they will have to make efforts to change their attitudes toward people, that they will have to treat their spouses decently, that their "depression" was not the root cause of their alcohol abuse, etc. Increasing the dose of fluoxetine does not appear to improve the increased dysphoria that accompanies these realizations. (One might speculate that this medication imparts a measure of insight.)

Happily, in our clinic we have happened upon a somewhat novel approach to this phenomenon: psychotherapy. Admittedly, we have had to resort to techniques regarded as "unscientific" by some leaders in the field (2), but we have found this approach to be of tremendous help.

Like others, we have seen some patients who have had excellent responses to fluoxetine, just as we have seen this with other antidepressants. Caution is urged for those prescribing fluoxetine; they should be on the alert for this paradoxical phenomenon.

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Fluoxetine and Suicidal Ideation

SIR: In a recent article, Martin H. Teicher, M.D., Ph.D., and colleagues (1) presented six case reports of patients who experienced increased suicidal ideation coincident with fluoxetine treatment. While acknowledging that this occurred in a "small minority" of their patients, they commented that "the purpose of this report is to suggest the surprising possibility that fluoxetine may induce suicidal ideation." In my opinion, this is not well substantiated and may introduce a medical-legal precedent.

Tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs) lack receptor specificity. These side effects (2) limit dose titration, patient compliance, and safety in somatic disease (e.g., cardiac disease) and represent a major concern about overdosage. In contrast, second-generation antidepressants are equally effective, are usually well tolerated, and exhibit a favorable therapeutic index. While any new treatment modality merits vigilance for unexpected sequelae, we should not lose sight of its beneficial addition to our therapeutic armamentarium (3).

One is struck by the multifaceted nature of each of the six reported cases (e.g., from EEG instability to borderline personality with atypical mood features). For this group of patients, impulsive behavior and refractory pharmacologic histories were the rule. Each patient had a history of suicidal ideation, and three had made suicidal gestures. The critical reader assumes that their medications were changed to fluoxetine because of worsening of mood. The concomitant medications (e.g., benzodiazepines) also confound analysis. In each case fluoxetine was not effective. In drug-refractory depression, enhanced vigilance for suicidal ideation is universally recommended. The response to MAOIs is not surprising, as the patients' profiles suggest superior outcome with them. The authors commented that "all [patients] were hopeful and optimistic" before taking fluoxetine. However, the case vignettes were not convincing in this respect. For example, in case 4, "before treatment with fluoxetine, Ms. D had relapsed into major depression" with "hypersomnia, social withdrawal, irritability, and psychomotor retardation."

The authors correctly pointed out that serotonin has a modulatory role in violent, suicidal, and obsessional behavior, and fluoxetine is "a potent and selective serotonergic reuptake inhibitor." The extreme complexity of the serotonin receptor system provides a theoretical framework for paradoxical reactions. However, the burden of proof is on controlled prospective studies. In the majority of patients, fluoxetine is both an effective antidepressant and a promising antiobsessional drug (4). Muijen et al. (5) compared fluoxetine, mianserin, and placebo in 52 patients with major depression according to the Research Diagnostic Criteria. Fluoxetine was associated with clinical improvement and no emergent suicidal tendencies.

In conclusion, the theory proposed by Dr. Teicher and associates is interesting, albeit preliminary and potentially counterproductive. The literature and clinical experience with fluoxetine do not support intense iatrogenic suicidal preoccupation in "3.5% of patients receiving fluoxetine." The authors advised clinicians to "query patients carefully about suicidal ideation, particularly if they are not responding well to treatment" (fluoxetine). Such advice is sage for all of us dealing with any depressed patient receiving any treatment modality. Inherent in the treatment process is informed consent, i.e., a relative risk-benefit analysis. The authors' inference that this drug should be used cautiously must be given critical review. Fluoxetine is, and likely will remain, a first- and/or second-line treatment of choice for major depressive disorder across a wide variety of patients. Even in the patient with suicidal ideation, we cannot lose sight of the inherent morbidity/mortality that follows tricyclic poisoning. Ongoing monitoring of suicidal potential is a cardinal point with any antidepressant.

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Dr. Teicher and Associates Reply

SIR: Dr. Tollefson expresses his opinion that our hypothesized association between fluoxetine and emergence of suicidal ideation is not well substantiated by our cases or by the literature and that our report is potentially counterproductive and may introduce a medical-legal precedent. First, from our perspective these cases were convincing. These patients had previously been treated with a large array of agents and medication combinations. At no other time had they developed such severe, unrelenting, and obsessive suicidal ideation. There was a very clear organic flavor to their apparent thought disorder, and this state eventually remitted in all cases after fluoxetine was discontinued and has not reemerged in four of the five patients that we continued to follow. Curiously, a similar suicidal state did emerge in one of these patients who was subsequently treated with clomipramine.

Second, support for our hypothesis is emerging in the literature. Fava and Rosenbaum (1) recently presented data on the emergence of suicidal ideation in 1,017 patients treated with a variety of antidepressants. In the patients without suicidal thoughts prior to treatment, suicidal ideation emerged in 3.5% during treatment with fluoxetine, in 6.5% during treatment with fluoxetine and a tricyclic, in 1% during treatment with tricyclics or a tricyclic and lithium, and in 0% during treatment with MAOIs. Thus, we continue to suggest that fluoxetine may induce suicidal ideation.

We are concerned by Dr. Tollefson's comment that our report may be potentially counterproductive and may introduce a medical-legal precedent. He appears to be arguing that we should not have published this report because our findings were preliminary, because fluoxetine is a highly selective drug with a low index of lethality, and because ongoing monitoring of suicidal potential is already a cardinal point in the treatment with antidepressants of any patient. These arguments are only superficially true and wither on deep reflection. First, the presumed neurochemical selectivity of fluoxetine is illusory. Yes, this agent binds specifically to the serotonin uptake port, but in doing so it affects serotonin turnover and postsynaptic receptors located on other neurotransmitter systems. The net effect is alterations in a number of neurotransmitters, including dopamine (2) and norepinephrine (3).

Second, is ongoing monitoring for suicidal potential really a cardinal point in the treatment of *any* patient with *any* antidepressant? We doubt that most nondepressed patients treated with antidepressants for obsessive-compulsive disorder, generalized anxiety, late luteal phase dysphoric disorder, attention-deficit hyperactivity disorder, Tourette's disorder, enuresis, migraine headaches, or weight control receive careful ongoing monitoring for the emergence of suicidal ideation. We are also concerned that the favorable therapeutic index of fluoxetine may lead to the increased use of this drug in patients with milder depressive diatheses who in the past may not have received antidepressant treatment, and many will undoubtedly be treated by nonpsychiatric physicians. We do not necessarily believe that these mildly depressed, nonsuicidal, low-risk patients will be carefully monitored for emergence of suicidal ideation, and the simple dosing strategy and low initial side effect profile of fluoxetine may inadvertently result in less frequent visits and less careful monitoring. We have now received information about the suicides of 10 patients. We are following up on these leads, but so far it appears that eight patients were at relatively low risk (e.g., were not affectively ill or had their first episode of mild to moderate outpatient depression although they had an intact family, a career, and ongoing treatment) before starting fluoxetine. We thus continue to urge caution in the use of this agent and suggest that patients be informed about this possible hazard.

There are three fundamental missions of academic medicine that prompted us to publish this preliminary report. These guiding principles are devotion to patient care, research, and teaching. The possibility that fluoxetine may produce a potentially life-threatening side effect made publication a necessity, as *primum non nocere* takes precedence over medical-legal concerns. Furthermore, research and discovery in psychiatry are highly interdependent and lengthy endeavors. The value of case vignettes is often to suggest a surprising new possibility. The success of a report lies in its ability to stimulate new research and to open our eyes to a new paradigm, so that eventually the truth may be learned. We believe that in this regard our report has been productive. It has stimulated fruitful debate and generated new research. Along with other reports (1, 4, 5) it introduces the concept of antidepressant-induced suicidal ideation. We think that this is a real phenomenon, but we lack definitive evidence. Rather than burying our heads in the sand to await further proof, we felt it important to risk being wrong and to tolerate criticism by our colleagues, in order to elicit their aid in researching this possibility both quickly and effectively.

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Cessation of Menses Due to Perphenazine Rather Than Fluoxetine?

SIR: With reference to the recent letter to the Editor "Reappearance of Menses in a Patient Taking Fluoxetine" by David V. Forrest, M.D. (1), there is an alternative explanation for the reappearance of menses in that patient based on the data provided in the report. The cessation of menses seems to have been due to perphenazine. While the author implied that fluoxetine was responsible for the reappearance of menses, a simpler explanation is that it was due to discontinuation of perphenazine. As the case report indicated, perphenazine had been discontinued when the patient started taking fluoxetine. This alternative inference is further supported by the fact that the patient's menses ceased again when she resumed taking perphenazine while continuing to take fluoxetine, and the menses reappeared when she stopped the perphenazine.

The report does serve the important function of alerting clinicians to keep in mind that changes in menstrual function may be due to psychotropic medications or their discontinuance.

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Dr. Forrest Replies

SIR: I agree with Dr. Viswanathan and associates. The patient's menses were suppressed when she was taking a phenothiazine (perphenazine) with and without the tricyclic (doxepin). When she was taking fluoxetine alone, the menses reappeared, whether or not they also would have appeared when she was taking no medication. My original report was entitled "Fluoxetine Flux" and noted that diarrhea, as well as menorrhea, appeared with the switch to fluoxetine. The diarrhea may have been caused by the decreased anticholinergic effect when perphenazine and doxepin were stopped, but also by the direct serotonergic action of fluoxetine on the gut. Fluoxetine also may not act purely on the serotonergic system and may indirectly mediate inhibition of dopaminergic neurotransmission (1, 2) with hormonal effects (3–5) that may affect the menses.

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Clozapine-Induced Weight Gain

SIR: We were pleased to see Seth Cohen, M.D., and associates' report on weight gain associated with clozapine in six of seven schizophrenic patients (1)—this despite a reported incidence of weight gain in less than 1% of 13,000 patients worldwide who had been treated with clozapine (2). However, their claim that this is the first report in the literature is not entirely accurate. Norris and Israelstam (3) reported that nine of 13 adolescent patients had experienced "an enormous and persistent increase in appetite, resulting in daylong compulsive eating." They reported weight gain of 10 to 20 kg within a period of 2 months of treatment.

This is a phenomenon we also have observed in a group of chronically mentally ill patients treated with this agent. We treated 21 patients with chronic psychosis and/or tardive dyskinesia and found that 14 (67%) gained >5% of their body weight at the time of starting clozapine, and eight (38%) gained >10% of their body weight. Some patients gained as much as one-third of their body weight and 50 lb. In our group, weight gain was significantly associated with improvement, as reflected by changes in total Brief Psychiatric Rating Scale (BPRS) scores, and with improvement in BPRS negative symptom subscales as selected by Kane et al. (4). We feel that clozapine-induced weight gain needs further study in light of the potential medical consequences of this problem and the possible insights into the neurobiology of schizophrenia that might be provided.

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SIR: The report of weight gain associated with the use of clozapine is of great interest. Recently, we reviewed the cases of five of seven patients treated with clozapine in the compassionate-use research phase. The average weight gained by these patients was 20.9 lb.

In researching the issue of weight gain associated with neuroleptics, we were able to locate several articles that reported similar weight increases in patients treated with clozapine. Simpson and Varga (1) reported an average weight gain of 9 lb, in comparison to a weight loss in placebo-treated patients. Povlsen et al. (2) reported that 12.9% of the patients treated with clozapine alone in their study had weight gain as a side effect. Lindström (3) reported that weight gain was a common but mild side effect. In their review, Bablenis et al. (4) reported weight gains of up to 24 kg per person during treatment with clozapine. The weight gain associated with clozapine treatment reported by Dr. Cohen and associates is well reported in medical literature.

The fact that weight gain is a side effect of neuroleptic treatment is well-known. The association of this side effect of neuroleptics with different mechanisms of action would appear to be a subject for further discussion.

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Dr. Cohen and Associates Reply

SIR: We appreciate the letters of Drs. Leadbetter and Vieweg and Dr. Carson and Mr. Forbes reporting the large percentage of clozapine-treated patients who gained weight. The literature they cite noted this side effect as early as 1975. However, in each case the weight gain was peripheral to some other central issue related to clozapine. In fact, since we submitted our manuscript, additional reports of weight gain associated with clozapine have been published by Lindström (1) and others. It has been noted previously that excessive weight gain associated with the use of antipsychotics may lead to noncompliance and a consequent return of psychotic symptoms (2). It was our intention to publish our experience with weight gain as a primary focus, since the attention until now, in terms of clozapine side effects, has been devoted to agranulocytosis and seizures. With an increased awareness of weight gain and compliance issues, it is our hope that clinicians can assist as many appropriate patients as possible to derive full therapeutic benefit from clozapine.

Both letters allude to the additional insights that study of weight gain with a novel agent might provide. Focusing on the serotonin S_2 blockade of clozapine and knowledge that the serotonin precursor tryptophan, the serotonin receptor stimulant fenfluramine, and the serotonin reuptake inhibitor fluoxetine are all capable of inhibiting weight gain, we gave 1–3 g of L-tryptophan daily to each of our patients and found that it had no effect on their weight gain. We agree that further study could add to our knowledge of the pathophysiology of schizophrenia.

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Differential Diagnosis and Treatment of Dementia

SIR: The study by George S. Zubenko, M.D., Ph.D. (1) showing "that determinations of the progression of illness did not distinguish patients with primary degenerative dementia of the Alzheimer type from those with multi-infarct dementia" is further evidence of the difficulty of differentiating before death these two important causes of dementia. Alzheimer's original paper also adds to this problem, as his patient had a fluctuating course and some focal symptoms, both of which are usually associated with multi-infarct dementia.

This difficulty in diagnosis was also mentioned by Perry and Markowitz (2), who noted that some types of multi-infarct dementia have an insidious onset and cannot be distinguished from Alzheimer's disease. These authors also mentioned, without giving references, the use of anticoagulant therapy as an alternative treatment for multi-infarct dementia. The theoretical value of anticoagulant therapy for multi-infarct dementia is very appealing, as it is logical to prevent an infarct by preventing its usual cause, the clotting of blood. Therefore, it would seem that the patient should be given the benefit of the doubt and offered a 4-month trial of anticoagulant therapy before being given up as having the hopeless Alzheimer's disease rather than a potentially treatable multi-infarct dementia. I feel that this is particularly so, because I have reported two patients diagnosed as having "presenile dementia" who responded well to an anticoagulant; one of them was later actually diagnosed at autopsy as having Alzheimer's disease (3). We should also remember that the two conditions may coexist, and lessening the cerebrovascular insufficiency with an anticoagulant could be quite beneficial.

In addition to my own frequent findings over the past 25 years of the lasting benefits of anticoagulant therapy in dementia (4), a controlled study by Ratner et al. (5), based on my published studies, demonstrated that not only did the anticoagulant prevent the progress of dementia in their patients, but it was safe, with no complications over the 1-year period of their study. I think their results would have been even better if they had added more psychiatric rehabilitative care to their program.

A recent literature search by the American Medical Association and the Menninger library services failed to reveal any studies showing that anticoagulant therapy was either unsafe or ineffective in dementia, so the only published studies are positive. All this seems to make it mandatory for the physician, when seeking informed consent from a dementia patient, to mention the possible inclusion of anticoagulant therapy in the treatment plan. Klerman (6) pointed out "the patient's right to effective treatment" and the psychiatrist's "responsibility to provide information as to alternative treatments" if the patient is not responding to present therapy.

As far as dementia of the multi-infarct or Alzheimer type is concerned, judging from the medical literature, anticoagulant therapy is the only reported potentially effective treatment. Besides many case reports, there has been one controlled study, and there have been no negative results reported. In addition, anticoagulant therapy has been noted to have long-lasting and even dramatic results in many patients, unlike ergoloid mesylates (Hydergine) and vasodilators, for which only minor and transient improvement has been claimed and for which there are many conflicting reports of even these benefits.

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SIR: In 1975 Hachinski et al. (1) adopted clinical criteria from Mayer-Gross et al.'s textbook of clinical psychiatry (2) to create an "ischemic score" for the differentiation of multi-infarct dementia from Alzheimer-type dementia. Rosen et al. (3) made an attempt to estimate the importance of the individual items of this so-called "Hachinski score" by comparing four patients with neuropathologically verified multi-infarct dementia to five patients with proven primary degenerative dementia and four patients with mixed dementia. The recent study by Dr. Zubenko made a new effort to evaluate the significance of an individual item (progression of illness) in 84 patients with clinically diagnosed dementia of the Alzheimer type and 40 patients with multi-infarct dementia. The major shortcomings of these studies were either the lack of a convincing number of patients (3) or the lack of neuropathological verification (Dr. Zubenko's study).

We would therefore like to draw attention to an earlier study without these flaws (4). It was based on meticulous clinical and neuropathological examination of 12 patients with "arteriosclerotic dementia." Alzheimer published his observations in 1895 and gave a concise outline of the relevant diagnostic criteria, i.e., his "ischemic score": abrupt onset ("sudden apoplectic attack"), stepwise deterioration ("course interrupted by further apoplectic attacks"), fluctuating course ("episodes of transient anxious excitement"), relative preservation of personality ("orderly conduct, preserved ability to reason"), depression ("hypochondriacal mood with deep insight"), somatic complaints ("cardiac and vascular symptoms"), evidence of associated arteriosclerosis ("always present"), focal neurological symptoms ("headache, vertigo"), and focal neurological signs ("tremor, paresis, reflex abnormalities, language disturbance").

Alzheimer's study suffered from two drawbacks. First, he did not use comparative statistics, although he intended to characterize multi-infarct dementia and to differentiate it from other forms of vascular dementia (perivascular gliosis, Binswanger's disease), degenerative senile dementia, and general paralysis. Second, the original version has not previously been accessible to English-speaking readers, although it represents the most likely empirical source of modern ischemic scores (1, 3, and the article by Zubenko), which has entered the United States through a psychiatric textbook written by authors who may still have been aware of Alzheimer's importance (2) and which is now reexported to Europe as "old wine in new bottles." Despite his numerous studies on vascular dementia, Alzheimer is better known for the disease which now carries his name. It would therefore probably be too confusing to rename the Hachinski score the Alzheimer score, even though this would be correct.

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Dr. Zubenko Replies

SIR: Dr. Walsh has been an advocate of anticoagulant therapy for the treatment of dementia for over 2 decades and has published several anecdotal reports describing positive results in patients with Alzheimer's disease (references 3 and 4 in his letter). However, I do not share his enthusiasm for this treatment modality because I do not agree with his characterization of the literature on the subject. In addition to his clinical experience, the only evidence that he *mis*cites in support of his position is a double-blind study of 14 institutionalized subjects with "senile and/or arteriosclerotic dementia," half of whom received sodium warfarin or placebo for 1 year (reference 5 in his letter). According to Ratner et al., in that study neither the placebo nor the anticoagulant drug proved to be a significant cause of variance in the dementia severity scores, and none of the large number of pairwise comparisons described in the manuscript reached statistical significance after correction for multiple comparisons was made (1). Moreover, the investigators found anticoagulant therapy to be "safe in carefully selected aged patients when proper precautions are used and there is regular hematologic and medical control," as was provided in their inpatient setting. Therefore, the results of that study may or may not be relevant to patients with Alzheimer's disease, they cannot be fairly characterized as positive, and the low frequency of side effects is unlikely to generalize to unselected elderly populations.

Perhaps the most troublesome of Dr. Walsh's comments is the suggestion that a physician's failure to recommend anticoagulation therapy as a treatment for Alzheimer's disease may represent substandard medical care. Alzheimer's disease is a tragedy from the perspectives of patients, family members, caregivers, and the nation as a whole. However, in my opinion, the diagnosis of a tragic disorder does not justify the prescription of a treatment of unproven efficacy without adequate regard for safety and potential side effects. Elderly patients who are cognitively impaired and prone to falling and who may be receiving treatment with medications that interact with anticoagulants are likely to be at high risk for complications. Even if a role for anticoagulant therapy in the treatment of Alzheimer's disease is eventually demonstrated, comparisons of anticoagulants to aspirin or related compounds may reveal an equally effective but safer approach.

The letter from Dr. Förstl and colleagues seems to serve largely to call attention to their translation of an article published by Alzheimer in 1895, which is said to describe "12 patients with atherosclerotic dementia." The translation was unavailable to me at the time that my response was invited, but I look forward to reading it when it is published. However, it is not clear from their letter why the Alzheimer reference was considered preferable to that of Rosen et al., who reported a clinicopathologic study of 14 cases of dementia (rather than 13, as cited in the letter). The stated reason for their preference is based on sample size but does not appear to be consistent with the relative sample sizes of these studies.

In my article, the characterization of the progression of dementia as "insidious" or "stepwise" did not discriminate between demented patients who met clinical criteria for Alzheimer's disease and those who had had two or more independent cerebrovascular accidents, as detected by neurologic examination and brain imaging. In fact, patients in the latter group were 3.7 times more likely to have experienced an insidious progression rather than a stepwise course. These results indicate that the retrospective characterization of the progression of dementia is of dubious diagnostic utility in the assessment of cerebrovascular disease among elderly psychiatric patients who suffer from primary dementia. The fact that the diagnosis of Alzheimer's disease was not made by histopathologic examination of brain tissue does not seem to detract substantively from this conclusion.

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Effects of Personality Disorder in Depressed Patients

SIR: In their article "Dysfunctional Attitudes in Depressed Patients Before and After Clinical Treatment and in Normal Control Subjects" (1), Eric D. Peselow, M.D., and colleagues highlighted the relationship between highly dysfunctional attitudes and poor treatment response, a finding with important clinical ramifications. The authors found that patients with particularly high Dysfunctional Attitude Scale scores responded poorly to pharmacologic treatment and suggested that particularly high scores on this scale may be an indication for nonbiological treatment modalities. Lower initial scores were found for patients who responded to pharmacologic treatment, and these scores generally decreased during treatment. Medication-responsive patients, however, still showed higher scores than did control subjects, a finding that the authors attributed to residual depression in some responders.

Perhaps because of the close theoretical link between dysfunctional attitudes and depression, this research (and, indeed, essentially all research on dysfunctional attitudes) fails to consider a critical variable: axis II diagnosis. In our study of 46 patients with borderline personality disorder (2), we found extremely high Dysfunctional Attitude Scale scores (mean=178.35), a finding that was independent of the presence or absence of current major depression. The presence of comorbid personality disorder, which has been associated with chronicity of depression (3) and poor treatment response (4–6), would provide a parsimonious explanation for the very high pre- and posttreatment scores of the patients with nonendogenous depression in the Peselow et al. study and the poor medication response observed in the patients with high scores.

It is apparent that the relationships among maladaptive cognitions, depression, and treatment response are likely to be much more complex than the literature suggests. It may be that dysfunctional attitudes are state-related in some individuals and recede with remission, whereas in other depressed patients with personality disorder, these attitudes are trait-related and inextricably tied to the chronic depression, dysphorias, and cognitive distortions that characterize these patients. Thus, the major depression may be successfully treated pharmacologically, but the personality disorder and the dysfunctional attitudes remain. Any future studies of the treatment of depression as well as of dysfunctional attitudes can ill afford to ignore axis II diagnosis.

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Sleep Disturbance in PTSD

SIR: In recent communications, Richard J. Ross, M.D., Ph.D., and associates (1) and Steven Lipper, M.D., Ph.D., and colleagues (2) speculated that a disturbance in the regulation of REM sleep is at the core of posttraumatic stress disorder (PTSD). Both groups cited evidence derived from drug treatments in support of this hypothesis—i.e., a decrease in intrusive symptoms and an improvement in sleep with antidepressant treatment. I recently treated two patients providing evidence counter to this view.

> Ms. A, a 40-year-old woman with PTSD stemming from a sexual assault, had a modest decrease in PTSD symptoms when given imipramine, 250 mg/day. The improvement included the reduction but not elimination of PTSD nightmares. After discontinuing drug treatment, she experienced intense short-term REM rebound and poorer sleep without a corresponding exacerbation in PTSD symptoms.
>
> Mr. B, a 41-year-old Vietnam veteran with severe PTSD, responded to fluoxetine, 60 mg/day, with a reduction in daytime intrusive symptoms, PTSD nightmares, and avoidance behavior. However, his overall sleep profile worsened considerably and included decreased total sleep time, shallower sleep, and increased daytime fatigue.

If the primary neurobiological diathesis in PTSD involves dysfunctional REM or even slow wave sleep, one might surmise that Ms. A's PTSD symptoms should have increased during discontinuation of the tricyclic antidepressant. Similarly, Mr. B's PTSD symptoms seemingly should not have waned as his sleep disturbance waxed under the influence of fluoxetine. The decrement in his PTSD nightmares is difficult to interpret, as both fluoxetine-induced sleeplessness and drug-related symptom improvement could have been contributory.

Glaubman et al. recently reported a case-control study of sleep in PTSD (3). Consistent with results of prior studies, PTSD subjects experienced poorer sleep, decreased sleep efficiency, increased awakenings, decreased slow wave sleep, and prolonged REM latency. Unfortunately, the authors were unable to study any of their subjects while they were having a PTSD nightmare. Thus, while it is probably safe to conclude that PTSD involves a mixture of REM and non-REM sleep pathology, it is less reasonable to infer that a disturbance in sleep regulation (4) is any more the hallmark of PTSD than are other features of the disorder, particularly reexperiencing and phobic avoidance (5).

What the field of traumatic stress studies needs at this point is less hypothesizing and more data. Fortunately, Dr. Ross, Dr. Lipper, and their colleagues correctly point us in this direction.

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Dr. Lipper and Associates Reply

SIR: We thank Dr. March for citing our communication to the *Journal*. However, he gives us too much credit in attributing to us the interesting, speculative hypothesis proposed by Dr. Ross and associates that dysregulation of REM sleep mechanisms may be implicated in some of the waking and sleep symptoms of PTSD. Our letter to the Editor was intended as a commentary on the article by Dr. Ross and his colleagues, not as an uncritical acceptance or endorsement of their hypothesis.

A closer reading of our letter will confirm also that we did not cite evidence derived from efficacy studies of medications in PTSD, as did Dr. Ross and associates, to support their hypothesis. On the contrary, we pointed out that in view of the divergent results of existing controlled studies, it is currently unclear how effective antidepressant medications are for PTSD, and for which symptoms. This point remains valid, as indicated by two additional controlled studies of the efficacy of medications in PTSD that have recently been published (1, 2).

The two case vignettes presented by Dr. March, while interesting and suggestive, are nevertheless inconclusive in the absence of polysomnographic recordings of the electrophysiological phenomena corresponding to the patients' subjective reports ("poorer sleep," "shallower sleep") and Dr. March's interpretations of their reports ("REM rebound"). Dr. March's discussion reemphasizes the necessity and importance of controlled sleep studies with polysomnography in well-defined groups of unmedicated and medicated patients with PTSD.

Although there may be truth to Dr. March's assertion that what the field of traumatic stress studies needs is less hypothesizing and more data, we believe that the formulation of testable hypotheses, even though they are speculative or provocative, is imperative, so that appropriate controlled studies can be designed and conducted to yield the kind of scientific data that will enhance our understanding of PTSD and its psychological and neurobiological bases.

While we have not proposed a "sleep disturbance" hypothesis, we have advocated a kindling hypothesis of PTSD supported by our finding in a small, uncontrolled study that carbamazepine was effective in selectively ameliorating the intrusive or reexperiencing symptoms of PTSD (i.e., recurrent nightmares, flashbacks, and intrusive recollections) (3, 4). According to such a hypothesis, the chronic central sympathetic hyperarousal associated with PTSD kindles limbic nuclei to produce a relatively stable neurobiologic abnormality. In our study, carbamazepine resulted in significant improvement not only in reported PTSD nightmares but in initial, middle, and late insomnia, as measured by the Hamilton Rating Scale for Depression. Of interest in this regard is the recent finding of Yang et al. (5) that carbamazepine significantly increased slow wave sleep and decreased REM sleep to 85.5% of baseline in seven unmedicated, healthy subjects after 9 days of treatment. However, a better understanding of the effects of carbamazepine on the sleep parameters of patients with PTSD must await future polysomnographic studies.

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Recovery From Bereavement After a Suicide

SIR: I appreciated the careful review of the sparse literature on bereavement after suicide by David E. Ness, M.D., and Cynthia R. Pfeffer, M.D. (1). The authors were particularly helpful in pointing out the problems in methodology in most of the research. Consequently, I was startled to see the completely unsupported statement that "these survivors never resolve their feelings entirely." Never? Any of them?

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Dr. Ness and Dr. Pfeffer Reply

SIR: If a person was attached emotionally to a deceased individual, then the feelings of loss persist for as long as he or she remembers that individual. In this general sense, such feelings are never resolved entirely. Rynearson, a psychiatrist whom we cited in our article, provided eloquent testimony about the persistence and the special quality of such feelings after the suicide of a loved one (1).

Our statement was not meant to disparage the ability of survivors to work through their grief but, rather, as we said, to caution against overly ambitious therapeutic goals.

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The Dissociative Disorders Interview Schedule

SIR: Marlene Steinberg, M.D., and associates recently made an important and welcome addition to the literature by publishing data on their Structured Clinical Interview for DSM-III-R Dissociative Disorders (SCID-D) (1). However, their article contains statements that deserve amplification and comment.

The first sentence reads, "Until now there has been no standardized instrument designed to yield uniform clinicians' diagnoses of the dissociative disorders." They later comment, "Current instruments specific to the dissociative disorders were designed as screening devices or symptom rating scales rather than as primary diagnostic instruments and are not meant to yield clinical diagnoses of dissociative disorders." In the final paragraph the authors state, "A uniform diagnostic instrument has not previously been available for use in large-scale epidemiologic or controlled pharmacological studies of the dissociative disorders."

We have developed a structured clinical interview called the Dissociative Disorders Interview Schedule which makes *DSM-III-R* diagnoses of the dissociative disorders. We first discussed this instrument with Dr. Steinberg in person in Chicago in 1986. Validity and reliability data on it were presented at a meeting Dr. Steinberg attended in 1987 (2). Data on the Dissociative Disorders Interview Schedule first appeared in the psychiatric literature in May 1988 (3), and further data were presented at a meeting in Chicago in 1988, which Dr. Steinberg attended. The Dissociative Disorders Interview Schedule is currently in the possession of more than 1,000 mental health professionals in North America. The complete schedule and its scoring rules are available in sources with 1989 publication dates (4, 5). Dr. Steinberg and Dr. Ross are both members of the Research Committee of the International Society for the Study of Multiple Personality and Dissociation, and the Dissociative Disorders Interview Schedule has been mentioned repeatedly in the correspondence of the committee. Both psychiatrists act as consultants on dissociative disorders to the Task Force on *DSM-IV*, and data on the schedule have been discussed by that committee.

We believe, therefore, that the statements by Dr. Steinberg and associates that we have quoted overlook information that was available to them and should like to correct the resulting inaccuracies in their presentation.

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Dr. Steinberg and Associates Reply

SIR: Dr. Ross and associates request amplification of several statements concerning the lack of a primary diagnostic instrument specific to the dissociative disorders prior to the development of the SCID-D. They go on to suggest that the Dissociative Disorders Interview Schedule might have been cited in this context. We stand by our original statements and believe that the citations requested by Dr. Ross and associates are not appropriate. At the time of publication of our article on the reliability and validity of the SCID-D, no article on the reliability and validity of their schedule for the five dissociative disorders had been published, and therefore no article on it was cited. The 1988 article for which Dr. Ross and his colleagues request citation made use of a variety of instruments to address issues other than instrument design, utility, and diagnostic validity. In fact, this article described overlap of symptoms in three cases of multiple personality disorder and three cases of obsessive-compulsive disorder. To date, information on the reliability and validity of the Dissociative Disorders Interview Schedule is still incomplete. No report has evaluated its utility as a primary diagnostic instrument for all of the five dissociative disorders.

In 1986 Dr. Ross attended the presentation by Steinberg and associates of data on the reliability and validity of the SCID-D, along with a description of the instrument, at the Third International Conference on Multiple Personality/Dissociative States (1). The SCID-D was developed and field tested prior to the development of the Dissociative Disorders Interview Schedule, and in 1986 Dr. Ross was familiar with the SCID-D instrument, the reliability and validity data, and the SCID-D research design. The first presentation of the Dissociative Disorders Interview Schedule was made in 1987 at the Fourth International Conference on Multiple Personality/Dissociative States, and at this time reliability was claimed only for 10 cases of multiple personality disorder, the most severe and chronic of the dissociative disorders, and no data were presented on the discriminant validity or interrater reliability for all of the five dissociative disorders.

Dr. Steinberg was on the advisory committee for the revision of the Dissociative Disorders section of *DSM-III* and is on the committee for revision of *DSM-III-R*. As researchers and clinicians know, reliability and validity of new diagnostic instruments are not established through this committee's work, nor is this the committee's task. It is also outside the scope of our research to speculate about the potential of the Dissociative Disorders Interview Schedule in light of inadequate assessment of fundamental psychometric properties. As information does become available we will be happy to cite and to respond to questions about the utility of this instrument. In conclusion, we stand by our statement that before the SCID-D there was no standardized instrument designed to yield uniform clinicians' diagnoses of the five dissociative disorders. We welcome peer evaluation of the SCID-D.

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Overemphasizing Diagnostic Classification

SIR: In a letter to the Editor (1), Mariam Cohen, M.D., complained about the reification and codification of the *DSM-III-R* diagnostic categories, especially by recent trainees. I think Dr. Cohen has touched upon a very serious problem in contemporary psychiatry. The labels we attach to phenomena are being treated as if they were the phenomena.

For roughly 15 years, APA has been preoccupied with classifying and reclassifying. This was not always the case. We always had a classification system, but it had not been the major concern that it has now become at the expense, one fears, of more basic considerations. All too often, to follow the direction of Dr. Cohen's thoughts, it has frozen rather than liberated our thinking. We study the diagnostic rule book instead of the patient.

This classificatory zeal has not been justified by a major breakthrough in our knowledge that would oblige us to revolutionize our diagnostic categories. Indeed, the changes that have been made are not revolutionary. On the contrary, they seem to be seeking a refinement that impresses some of us as excessive.

No doubt, multiple factors have contributed to this preoccupation with classification. The advent of lithium probably stimulated the upsurge in the diagnosis of affective disorders at the expense of schizophrenia. But our pharmacotherapeutic agents are not so diagnosis-specific as we sometimes think; lithium has been advised as an adjuvant in the treatment of schizophrenia.

The greater role that third-party payments play increases the need to seek additional diagnostic categories, although not constantly to revise them. We may require diagnoses for billing purposes; but that should not lead us to grant them transcendental significance nor cause us to reify processes.

I feel that the result has been an unfortunate overvaluation of diagnostic niceties. It is dangerous to take the creation of our collective mind for the phenomena that we should be studying. We may have to redefine and recategorize our material as new basic discoveries occur. To take our present classification too seriously could be an obstacle to progress.

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Efficacy of Psychotherapy

SIR: I commend Stephen Fleck, M.D., on his letter (1) in which he reiterated the importance of psychiatrists' learning about patients through professional involvement over time and treating them as persons with complex problems rather than containers of malfunctioning machinery. I also commend the joint task force of the Association for Academic Psychiatry and the American Association of Directors of Psychiatry Residency Training for stressing the importance of training in psychodynamic psychotherapy.

I could not help noticing that there was a spate of letters criticizing the recommendations, especially the emphasis on the primacy of learning psychodynamic psychotherapy. Somehow, it was misinterpreted that this primacy would exclude or unduly subordinate other schools of thought and that this primacy goes against the lack of statistical proof of psychotherapy's efficacy.

It is true that there is no statistical proof of the efficacy of psychodynamic psychotherapy. Psychotherapy researchers have been unable to control the variables sufficiently to demonstrate its efficacy in comparison with control groups. This fact will be unchanged but is basically irrelevant. To paraphrase Thomas Jefferson, there are certain truths which are self-evident. So far, there is not convincing proof that democracy is superior to totalitarianism or that education is superior to ignorance.

It should be a given, by now, that the long-term study of a person, using psychodynamic concepts and a stance of being a participant-observer with an individual over time, is the best way we know of understanding the complexity of a person in depth and breadth. This is the wisdom of the ages as it has ripened in the twentieth century. The detractors of psychodynamic psychotherapy speak with knowledge but lack a certain wisdom.

It is reassuring to one who has practiced and taught for 40 years to see that the vision of wisdom clears a path through the fog of what passes for knowledge.

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Reprints of letters to the Editor are not available.

Report of the APA Task Force on Prevention Research

This report was prepared by the Task Force on Prevention Research[1] of the Council on Research. It was approved by the Board of Trustees in June 1990.

DEFINITIONAL DIFFICULTIES

This report is a review of research on the prevention of psychiatric disorders. Although there are a few articulate and productive researchers in this field, in general prevention research in psychiatry has not commanded much attention or achieved great credibility. It is not perceived as a "hot" area of research, and currently it is not viewed as providing much of practical value in treatment.

At the same time, much of the budget for the National Institute of Mental Health (NIMH) is justified in terms of the ultimate relevance to prevention of the research being supported. This is certainly appropriate, since prevention strategies are based on our understanding of causal mechanisms. In addition, it could be argued that any substantial increase in our knowledge of disorders or diseases that impair our emotional, behavioral, or cognitive function has real potential in preventing these disorders. However, this perspective is broader than what is generally considered the domain of prevention research itself and includes areas that have only the potential of becoming the focus of prevention research in the future.

This review will focus on current prevention research in psychiatry and some past efforts. Our discussion is guided by the U.S. Public Health Service definition: "Prevention research includes only that research designed to yield results directly applicable to interventions, to prevent occurrences of disease or disability, or to the progression of detectable but asymptomatic disease."

Many authors have pointed out that our field's claims about prevention have a troubling history, that promises have been unfulfilled and conclusions have been stated without sufficient empirical evidence. Pardes et al. (1) stated,

> During the first half of the century, primary prevention was achieved with traditional public health approaches for at least two illnesses with psychiatric components: pellagra and general paresis. The discovery that infection with measles, during a woman's first trimester, puts the fetus at risk for brain dysfunction also resulted in the application of primary prevention techniques for women in their child-bearing years. In the past decade, with new techniques (including methods developed by other disciplines, such as neurology and genetics), psychiatric epidemiologists have been working to identify antecedent factors that may provide a basis for other primary prevention strategies.
>
> Nevertheless, the application of public health methods to mental health problems has been a complex proposition. The classic public health model, conceptualizing illness in terms of host, agent, and environment, does not "fit" most psychiatric disorders. The difference now, in psychiatry and behavioral science, is the mounting evidence for a biological substrate in many mental disorders. Environmental and social factors are now regarded—more widely than in the past—as critical determinants of whether an illness will be expressed in a biologically vulnerable individual, rather than as exclusive causes in themselves. Recognizing this distinction may make public health approaches, both to major mental illnesses and to behavioral dysfunctions, much more feasible. Connections among biology, environment, and psychopathology can be analyzed in much more specific terms. Such specificity can, it is hoped, move psychiatric prevention research into the mainstream of public health research, training, and service.

It is our belief that a review of what went wrong in the past in prevention research in psychiatry will clarify and highlight today's much more solidly based research, which is an exciting and promising field.

PAST PREVENTIVE INTERVENTIONS

As Shaffer (2) has pointed out, for most of the last 100 years there has generally been a humane and optimistic view about preventing children's unhappiness and disturbed behavior. However, it is also true that until recently, any psychiatric disorder in a child was predominantly viewed solely as a distortion of normal development. Thus, it was held that if parents avoided being too repressive, thus preventing the child's expression of normal wishes or impulses, and if they attended to the principles of learning theory and reinforcement, their child would not develop significant disturbances or psychopathology. Later it was felt that if parents could be educated more intensively, if prenatal care could be extended to all women, and if parents and children had more access to medical resources and housing, a happy and productive childhood would almost universally be ensured. However, as pointed out by Eisenberg (3), the "IOUs" issued in the early days of the mental hygiene movement, which promised that "mental illness" would be eliminated by education about human relationships, proved to be unredeemable. Thus, some of the widespread disbelief or skepticism regarding preventive psychiatry can be traced directly to early assertions that preventive interventions such as education, support, and reasonable child-rearing practices would together prevent child psychopathology.

Risk for Illness

As Shaffer (2) also pointed out, mental health professionals are now generally skeptical about true primary prevention of any disorder. That is, we do not know how to prevent the initial appearance of any psychiatric disorder, with the exception of certain disorders of childhood. There is also a developing consensus in our field that most disorders cannot be explained solely as the result of stresses imposed on normal developmental processes. This model was essentially founded on the belief that all individuals have a universal potential for disturbance, and it de-emphasizes or ignores the observation that some people are at substantially greater risk for specific disorders than are other people.

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[1] The members of the Task Force on Prevention Research are Robert M. Rose, M.D. (chairperson), Felton Earls, M.D., Sheppard Kellam, M.D., Daniel Offer, M.D., Irving Philips, M.D., and Morton Silverman, M.D.

The concept of universal, nonspecific vulnerability for illness is no longer widely held in psychiatry; we have learned from a number of excellent studies that there are significant differences in vulnerability to certain psychiatric disorders. Earls (4, 5) has divided the data about differential risk into two types of epidemiologic studies. The first type addresses the prevalence of disorders in parents and other adult relatives of children, and the second is longitudinal studies of impaired children that evaluate the risk for later development of adult disorders. Both types of studies have contributed greatly to our understanding of risk factors in vulnerable children.

Nevertheless, it is also clear that many mental health professionals mistrust the medical-illness model of child and adolescent psychopathology. There is tension between those who focus on specific risk factors as antecedents for psychopathology and those who do not support this specific-etiology model. The latter group finds that an antecedent-condition model applies across a wide range of emotional and behavioral dysfunctions. These observers argue that nonspecific predisposing factors and precipitating conditions may be responsible for the expression of many disorders, moving away from the focus on specific risk factors to the possibility of a more universal potential for disturbance in various populations. Felner and Silverman (6) stated,

> At this point, a key debate in the prevention literature becomes salient if we are to decide how and when to move from "risk factors" to programs. We need to be clear on how we answer the questions: a) Do we attempt to tailor primary prevention programs to the prevention of a specific disorder, or b) do we develop programs which are effective in alleviating a number of conditions that are antecedent to a range of emotional and physical problems, including, but not limited to the target problem?
>
> The "specific disorder prevention" model rests heavily in a classic medical-public health paradigm which views diseases as caused by specific conditions that interact with individual vulnerabilities, again, specifiable. In contrast, the antecedent condition model argues that at least for a wide range of emotional and behavioral disorders, particularly those related to stress and other elements of the normal life-course, the specific etiology model is not appropriate.

Types of Interventions

Another way of characterizing this tension between the models focusing on general vulnerability and on specific risk factors was summarized by Pardes et al. (1), who suggested it may be useful to divide prevention efforts into universal and selective or indicated.

Universal preventive interventions are directed at an entire population and not specifically at subgroups presumed to be at greater risk. Examples of such efforts are fluoridation of water, vitamin supplementation of milk and bread, and immunization of infants for various infectious diseases. These clearly are effective preventive interventions. The difficulty in psychiatry is whether or not recommendations based on the universal model, i.e., applying to all groups, are at all effective. Educating parents, providing more information about childhood anxieties, and providing more adequate schooling in general are examples of universal interventions that have not been shown to affect the incidence or prevalence of specific psychopathology. That is not to say, however, that many children have not benefited from such strategies. It would be reasonable to conclude that *promoting better mental health practices clearly has substantial benefits, but it has not been shown, nor is it believed, that these general measures substantially affect the appearance of child psychopathology, without a more specific, targeted approach in vulnerable individuals.*

Selective, or indicated, interventions are directed at individuals who are at greater risk for diseases or disorders than the general population. One example is the demonstrated effectiveness of Project Head Start. As pointed out by Eisenberg (3), despite earlier negative findings about Project Head Start, which were based on flawed research strategies, recent evidence has shown impressive support for the program's effectiveness—specifically, better school progress, fewer dropouts, less delinquency, and better work records after high school. Individuals with demonstrated need, primarily because of lower socioeconomic status or fewer resources, clearly benefited by participation in Project Head Start.

Project Head Start is a selective intervention that provided clear improvements in several outcomes, but it has not been shown to affect specific psychopathology. Some selected interventions have not been effective and may have contributed to the skepticism about preventive interventions for psychiatric disorders or mental illness in general.

Eisenberg (3) reviewed the Cambridge-Sommerville Delinquency Prevention Project, which was one of the largest undertakings of its kind and operated from 1938 to 1945. Its design incorporated the accepted interventions of the day—individual guidance, counseling, and case work therapy—which were provided to several hundred underprivileged boys. The project fortunately did include a control group, and the results showed no significant differences between the control subjects and the group that received the therapies. Also troubling was the finding 30 years later by McCord (7) that the boys who had the counseling may have done worse than the control group. This targeted intervention, designed to diminish the prevalence of delinquency (judged according to number of repeated offenses, incarceration, etc.), failed to produce its presumed effect. It is not clear whether the focused intervention was for all individuals with a given socioeconomic status or for those who showed some significant dysfunction. In any event, *it casts doubt on the assumption that any form of positive, well-intended therapeutic intervention can be of benefit.*

Premature Applications

Another problem in earlier prevention research in psychiatry was the premature translation of theory to practice, without the data necessary to document the efficacy of the approach. One example of this was the assumption of the crucial importance of mother-infant bonding. Proponents of this view argued that the first minutes or hours of life are a sensitive period and that the father and/or mother must have close contact with the infant during this time to ensure that its later development will be optimal. Even though there was not compelling evidence for the necessity of a correct form of early bonding for later normal development, this became translated into dogma, which later research did not substantiate. Some parents feared that they might have lost an irretrievable opportunity by failing to bond adequately with their child, thus adversely affecting their child's development.

CURRENT PREVENTION RESEARCH

Our current knowledge of prevention in psychiatry is derived from robust epidemiologic findings. It focuses on specific risk factors and, most important, on manipulating or altering these risk factors so as to diminish the frequency of occurrence of the disorder. Studies that attempt such experimentation are often referred to as "experimental epidemiology" or "applied epidemiology" and usually involve a trial of a preventive intervention. In fact, some have suggested that, given the varying negative connotations of the term "prevention," this area of research should be renamed "applied epidemiologic research."

Research involving preventive interventions focuses on two questions: Is it possible to change a particular risk factor? and Does such a change, once effected, make any difference in outcome or incidence of future illness?

As Earls (4) has pointed out, confusion has also arisen because risk factors have not been restricted to causes or even correlates of the disorder; erroneously, even consequences have been designated as risk factors. Furthermore, attributes such as age and sex have been designated risk factors. Appropriate use of the term "risk factors" is most important when one moves from descriptive studies to experimental interventions, where risk factors should be restricted to variables that can be manipulated (attributes usually cannot be manipulated).

Prevention research in psychiatry has progressed substantially from assertions of causal relationships based solely on theoretical positions and not on solid epidemiologic, prospective, or longitudinal data. Our data have been gathered from complementary studies of the most salient risk factors in various mental disorders, but they are uneven. We have more complete information about childhood conduct disorder and adult antisocial behavior than about affective disorders or schizophrenia. However, this unevenness of solid data across the diagnostic spectrum is no worse in psychiatry than it is in other medical specialties.

Because there is more consistent information regarding how childhood conduct disorder functions as a significant risk factor for adult antisocial behavior and substance abuse, attempts to modify the onset of childhood conduct disorder have moved to the forefront of research on preventive interventions in psychiatry.

A brief review of this research will exemplify the strength and sophistication of current prevention research in psychiatry and will explain our enthusiasm about this field. It will also emphasize the need for more attention and support for psychiatric prevention research.

CHILDHOOD CONDUCT DISORDER

Of all the disorders that might be prevented, childhood conduct disorder should be a prime target, for reasons that were stated most compellingly by Eisenberg (8) almost 25 years ago:

> There remains, however, the highly significant finding that it is the child with antisocial behavior who presents the highest risk for psychiatric disability in adult life; this stands in glaring contrast to the traditional child guidance bias in favor of supplying treatment to the neurotic child, the child whose prognosis appears so much better even without treatment. This is not to suggest that we rush forth to "treat" the sociopath (since there is no evidence that customary therapeutic measures have any impact on him), but rather that we accept the challenge to devise and to evaluate new methods for intervention in the face of what is clearly an overwhelming public health problem.

Research conducted since that time supports Eisenberg's conclusions, and it is reasonable to conclude "that childhood conduct disorder and its adult outcome represent one of the most important public health problems in psychiatry" (5).

The classic work of Robins (9) demonstrated the continuity of aggressive and antisocial behavior from childhood to middle adulthood. This work was replicated by Olweus (10) and Heusmann et al. (11). Gittelman et al.'s longitudinal study (12) confirmed the finding that hyperactive children have a high probability of becoming antisocial and drug-abusing adults. However, although half of the hyperactive children in their study developed these adult disorders, almost half the children in this high-risk category did not.

Research has clearly demonstrated that childhood conduct disorder is associated with a significant risk for adult psychopathology, and there is strong evidence for significant family transmission or clustering of conduct disorder, attention deficit disorder, and oppositional behavior.

Since it has been demonstrated that conduct disorder is associated with a significant risk for adult psychopathology, we must ask whether or not it is changeable, i.e., Can conduct disorder be altered? If so, Will the diminution in conduct disorder be followed by a decrease in adult antisocial behavior? Will it make a difference?

We discuss this area of prevention research in detail only to illustrate current thinking; other areas in psychiatry are also progressing and involve strategies derived from solid epidemiologic findings. The disorders being studied include posttraumatic stress disorder following catastrophes and psychopathology in children of psychiatrically ill parents. Research in these areas may lead to development of intervention strategies focused on those at risk.

The possibility that development of childhood conduct disorder can be changed by systematic manipulation of the child's environment derives from work demonstrating that the appearance of conduct disorder in children is preceded by clear differences in play behavior and peer interactions between these children and children who do not develop conduct disorder. Thus, conduct disorder can be viewed as an outcome later in childhood of earlier differences in behavior. It is important to keep in mind, however, that even if interventions are successful and we are able to diminish the incidence of childhood conduct disorder, it still remains to be demonstrated that these interventions will lead to a fall in the rate of adult antisocial behavior.

Behavioral Antecedents

Kellam et al. (13) have studied four cohorts of first-grade children and followed them to the third grade; one cohort was followed to age 16 or 17. Aggression coupled with shy behavior—defined as sitting alone and not participating in the classroom but also fighting and breaking rules—was shown to predict conduct disorder and, in individuals followed to age 16 or 17, adolescent antisocial behavior.

Aggressive behavior in a first-grade child can be considered a maladaptive behavioral response to the teacher's demands that the child accept authority, i.e., not fight, disrupt activities, or break rules. In addition, shy behavior can be considered a maladaptive behavioral response to the tasks of participating in the classroom teaching and interacting with classmates.

If shy behavior and aggression are clear antecedents of later conduct disorder, attempts to change such behaviors might lead to a decrease in conduct disorder.

Research from education and developmental psychology has also demonstrated that preschool interventions have benefits for later school success. These findings have encouraging implications for preventive interventions applied specifically to the predictors of conduct disorder. Earls (5) summarized 18 experiments which showed that preventive interventions significantly reduce the need for special education, lower the dropout rate, increase vocational placement, etc.

Two major studies of preventive interventions in conduct disorder are currently being conducted. They are attempting to prevent conduct disorder in children and demonstrate that modifying the onset of conduct disorder leads to diminution in adult psychopathology.

The Prevention Center of the Department of Mental Hygiene at Johns Hopkins University has established a preventive intervention trial in the public schools in Baltimore. In each school, the students in one first-grade class receive a mastery learning intervention, which enhances learning skills, and in a matched first-grade class the students are instructed in a good-behavior game, which attempts to diminish the frequency of aggression. Classes not receiving any intervention serve as control subjects.

The active intervention was the good-behavior game, in which the children receive points for precisely defined good behavior and demerits for shy or aggressive behavior. The mastery learning intervention individualizes learning by defining precisely what the students should learn, establishing confidence even when the children have learning difficulties.

Teacher ratings, school records, peer nominations, and behavior observations are used to measure social adaptation status. A preliminary data analysis showed that students who participated in the mastery learning intervention gained 12 percentile points and students who did not receive this intervention either declined or stayed the same. The good-behavior game also produced an effect on its target outcome—aggressiveness ratings by classmates. The aggression ratings for both boys and girls were significantly lower in the classes that played the good-behavior game than in the control classes in the same schools.

Although these experiments in the Baltimore school system do not specifically examine the frequency of childhood conduct disorder, it seems likely that if learning improves and aggressive behavior decreases, fewer students will be diagnosed as having conduct disorder, although this has not yet been conclusively demonstrated.

Another study of preventive intervention in conduct disorder is being planned by the Program on Human Development and Criminal Behavior at the Harvard School of Public Health, which is receiving support from the National Institute of Justice and the MacArthur Foundation. This program is in the planning phase, and a number of research design areas are being explored, including the following.

1. An accelerated longitudinal design using cohorts with overlapping age ranges.

2. Systematic assessment of the child's biological family and of psychosocial risk factors in the first 5 years of life.

3. Measurement of conduct disorder, delinquency, criminality, and related behaviors in adolescence and young adulthood.

4. The study of different neighborhoods to understand how biological and psychosocial risk factors combine to produce community variation in serious crime.

5. Formal experiments to reduce the incidence of conduct disorder and delinquency.

It appears that we can modify aggressive and shy behavior and improve learning in children. It has not yet been established whether or not these outcomes diminish the frequency of conduct disorder among the children who participate in these interventions. Since research must first demonstrate that these interventions lead to a decreased incidence of conduct disorder, it is too soon to know whether they are followed by diminished adult antisocial behavior or substance abuse.

Nevertheless, this research is well designed and is based on results from epidemiologic findings, and it is an excellent example of specific interventions that have significant potential for altering the appearance of childhood psychopathology and, possibly, adult psychopathology.

In summary, it is our conclusion that prevention research in psychiatry has come of age. Current research efforts are derived from solid information gathered from a variety of epidemiologic studies demonstrating the existence of risk factors in at least one major area of psychopathology. Studies are now focusing on manipulation of specific risk factors designed to significantly decrease the development of major psychopathology. Should such research indicate that preventive interventions are effective, the field could certainly argue for larger trials aimed at diminishing the frequency of conduct disorder.

RECOMMENDATIONS

The promise of prevention research in psychiatry should be much better disseminated in the field and the potential for research studies should be communicated more broadly to the psychiatric research community. The task force recommends the following strategies for achieving these goals.

1. There is a need for more focus on preventive intervention research during the APA annual meeting. The possibilities include a special poster, oral/slide, or other type of session and special-interest group meetings.

2. A supplement or special section in the *American Journal of Psychiatry* or other APA publication would increase awareness of prevention research findings and opportunities. The topics should include an overview of the field, current studies, and a review of relevant epidemiologic research.

3. APA components should give higher priority to research on preventive intervention, affording more extensive discussion and action. The components to which this work is relevant include the Council on Psychiatric Services, the Council on Children, Adolescents, and Their Families, the Council on Medical Education and Career Development and its components (especially the Committee on Graduate Education), the Scientific Program Committee, and the Council on Research and its components (particularly the Committee on Research on Psychiatric Treatments and the Committee on Research Training). In addition, the newly formed Council on Addictions and the Committee on AIDS should pay special attention to prevention research, particularly given its potential importance in these areas and the strong interest of NIMH, the National Institute on Drug Abuse, and the National Institute on Alcohol Abuse. Finally, the Council on Aging should pay special attention to prevention of mental illness in the elderly and to methods for encouraging successful aging. The Joint Commission on Government Relations should monitor the efforts described in item 4.

4. The Alcohol, Drug Abuse, and Mental Health Administration and its three institutes should ensure that there is an appropriate psychiatric perspective in the prevention research programs, in development of new programs, in their budgetary support, and in their review. Psychiatrists who are active in research in these areas should serve as committee members. Their involvement would help ensure focus on a) the more severe mental disorders and b) an appropriate epidemiologic framework for the experimental research.

In summary, prevention research in psychiatry now has a strong empirical base and focuses on manipulating specific risk factors in order to significantly decrease the development of major psychopathology.

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Following is the comprehensive index for volume 147 of the *Journal,* which covers all material in January 1990 through December 1990. The complete citation for each article in the author index is listed under the name of the first author. Coauthors are listed alphabetically with a cross-reference to the first author; cross-references containing multiple first author names separated by semicolons indicate multiple articles by the coauthor. Book reviews appear in the author index under the name of the reviewer and in the subject index under the heading Books Reviewed; the books reviewed are arranged alphabetically by the surname of the book's first author or editor. In addition to being indexed by author name, letters to the Editor regarding articles published in 1990 are indicated in parentheses after the citations for those articles.

Each entry in the subject index is identified by the surname of the first author only; semicolons between names of authors of letters to the Editor indicate multiple letters. Two-letter abbreviations are used for months. Entries other than Special Articles, Regular Articles, Commentaries, and Clinical and Research Reports are given the following designations: editorial (editorial), In Memoriam (in mem), book review (bk rev), letter to the Editor (letter), and Official Actions (off acts). Corrections are cited with the articles to which they refer and under the heading Corrections in the subject index.

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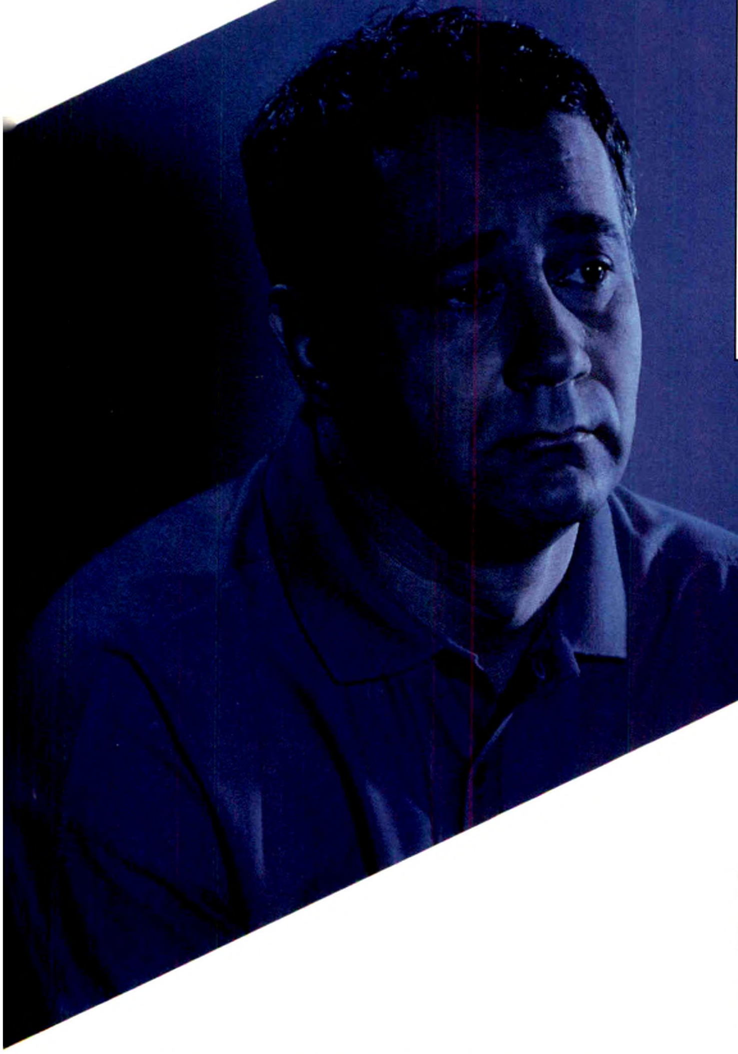
* Prozac is a registered trademark of Dista Products Co., a division of Eli Lilly and Company.

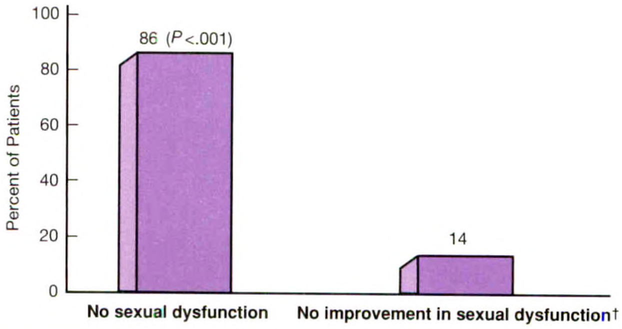
Bill's doctor wants a new-generation, non-serotonergic antidepressant that also minimizes risk of sexual dysfunction...

- Because WELLBUTRIN may cause little sexual dysfunction, it may improve patient compliance.[1]



Relieves depression with fewer adverse effects on sexual performance

Male Patients Switched to WELLBUTRIN Who During Previous Antidepressant Therapy Experienced Sexual Dysfunction (N=28)[1]*



Start with non-serotonergic

Wellbutrin®

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Relieves depression with few life-style disruptions

*Impairments that ceased to occur after treatment with WELLBUTRIN were decreased libido, decreased erectile capacity, or delayed or retrograde ejaculation. Patients were receiving tricyclic antidepressants prior to switching to WELLBUTRIN.

†Of the four patients (age range: 50 to 67) who demonstrated no change in sexual dysfunction, two were diabetic and two had lifelong histories of sexual disability.

The man whose medication caused sexual dysfunction

Name: Bill – Occupation: Unemployed administrative assistant
Age: 48 – Height: 5'10" – Weight: 170 lb

History

Patient complains of fatigue, inability to concentrate, and feelings of worthlessness since staff cuts at the corporation where he worked for 21 years resulted in the loss of his job. He has failed to begin company-sponsored job retraining program and to look for a new job.

Diagnosis: Depression

Initial treatment

After 2 months of antidepressant treatment, patient complains of sexual dysfunction (erectile failure and decreased libido), which had not been a problem prior to antidepressant treatment. Although patient's depression has improved, he insists the medication is causing the sexual dysfunction and requests that medication be discontinued.

Recommendation

Discontinue current antidepressant and switch to a new-generation, non-serotonergic antidepressant. Start WELLBUTRIN to relieve depression and minimize risk of sexual dysfunction.

Outcome

After 4 weeks of therapy with WELLBUTRIN, patient reports feeling more energetic. Sexual performance is normal. He has enrolled in job retraining program.

See brief summary of full prescribing information on last page of this advertisement.

Every day doctors are choosing WELLBUTRIN instead of Prozac®* (fluoxetine HCl).

WELLBUTRIN is a unique new-generation antidepressant that:

- Effectively relieves depression with few life-style disruptions
- Is non-serotonergic[2-5]
- Has few cardiovascular effects[6-8]
- Causes few anticholinergic effects[3,9]
- Causes little or no weight gain[3,10]
- Causes little or no daytime drowsiness[9]
- Has minimal risk of sexual dysfunction[1]

The principal medically important adverse reaction with WELLBUTRIN is seizure, which occurs in approximately four-tenths of one percent of patients. This incidence may exceed that of other marketed antidepressants, although no direct comparative studies have been conducted. For more information about dosing to achieve optimal patient response and recommendations for reducing the risk of side effects, see full prescribing information, especially the DOSAGE AND ADMINISTRATION and WARNINGS sections.

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1. Gardner EA, Johnston JA. Bupropion—an antidepressant without sexual pathophysiological action. *J Clin Psychopharmacol.* 1985;5:24-29. **2.** Shea VK, Wang CM. Bupropion (Wellbutrin) inhibits the firing rates of noradrenergic but not serotonergic neurons. *Soc Neurosci.* 1985;II:185. Abstract. **3.** Data on file, Burroughs Wellcome Co., 1990. **4.** Ferris RM, Cooper BR, Maxwell RA. Studies of bupropion's mechanism of antidepressant activity. *J Clin Psychiatry.* 1983;44(5, sec 2):74-78. **5.** Richelson E. Synaptic pharmacology of antidepressants: an update. *McLean Hosp J.* 1988;XIII:67-88. **6.** Farid FF, Wenger TL, Tsai SY, Singh BN, Stern WC. Use of bupropion in patients who exhibit orthostatic hypotension on tricyclic antidepressants. *J Clin Psychiatry.* 1983;44 (5, sec 2):170-173. **7.** Roose SP, Glassman AH, Giardina EGV, Johnson LL, Walsh BT, Bigger JT Jr. Cardiovascular effects of imipramine and bupropion in depressed patients with congestive heart failure. *J Clin Psychopharmacol.* 1987;7:247-251. **8.** Wenger TL, Cohn JB, Bustrack J. Comparison of the effects of bupropion and amitriptyline on cardiac conduction in depressed patients. *J Clin Psychiatry.* 1983;44(5, sec 2):174-175. **9.** Lineberry CG, Johnston JA, Raymond RN, et al. A fixed-dose (300 mg) efficacy study of bupropion and placebo in depressed outpatients. *J Clin Psychiatry.* 1990;51:194-199. **10.** Harto-Truax N, Stern WC, Miller LL, Sato TL, Cato AE. Effects of bupropion on body weight. *J Clin Psychiatry.* 1983;44(5, sec 2):183-186.

The patient depicted in this advertisement is not an actual patient, but is a fictional composite of typical patient types.

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(BUPROPION HCl)

Relieves depression with few life-style disruptions

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WELLBUTRIN® (BUPROPION HYDROCHLORIDE) Tablets

Before prescribing, please consult complete product information, a summary of which follows:

INDICATIONS AND USAGE: Wellbutrin is indicated for the treatment of depression. A physician considering the initiation of Wellbutrin should be aware that the drug may cause generalized seizures with an approximate incidence of 0.4% (4/1000). This incidence may exceed that of other antidepressants as much as fourfold. This relative risk is only an approximation since no direct comparative studies have been conducted.

CONTRAINDICATIONS: Wellbutrin is contraindicated in patients: with a seizure disorder; with a current or prior diagnosis of bulimia or anorexia nervosa, because of a higher incidence of seizures noted in such patients; who have shown an allergic response to it; or who are currently being treated with an MAO inhibitor. At least 14 days should elapse between discontinuation of an MAO inhibitor and initiation of treatment with Wellbutrin.

WARNINGS: SEIZURES: Wellbutrin is associated with seizures in approximately 0.4% (4/1000) of patients treated at doses up to 450 mg/day. This incidence of seizures may exceed that of other marketed antidepressants by as much as fourfold. This relative risk is only an approximate estimate because no direct comparative studies have been conducted. The estimated seizure incidence for Wellbutrin increases almost tenfold between 450 and 600 mg/day, which is twice the usually required daily dose (300 mg) and one and one-third the maximum recommended daily dose (450 mg). Given the wide variability among individuals and their capacity to metabolize and eliminate drugs, this disproportionate increase in seizure incidence with dose incrementation calls for caution in dosing.

During the initial development, 25 among approximately 2400 patients treated with Wellbutrin experienced seizures. At the time of seizure, 7 patients were receiving daily doses of 450 mg or below, for an incidence of 0.33% (3/1000) within the recommended dose range. Twelve (12) patients experienced seizures at 600 mg per day (2.3% incidence); 6 additional patients had seizures at daily doses between 600 and 900 mg (2.8% incidence).

A separate, prospective study was conducted to determine the incidence of seizure during an 8 week treatment exposure in approximately 3200 additional patients who received daily doses of up to 450 mg. Patients were permitted to continue treatment beyond 8 weeks if clinically indicated. Eight (8) seizures occurred during the initial 8 week treatment period and 5 seizures were reported in patients continuing treatment beyond 8 weeks, resulting in a total seizure incidence of 0.4%.

The risk of seizure appears to be strongly associated with dose and the presence of predisposing factors. A significant predisposing factor (e.g., history of head trauma or prior seizure, CNS tumor, concomitant medications that lower seizure threshold, etc.) was present in approximately one-half of the patients experiencing a seizure. Sudden and large increments in dose may contribute to increased risk. While many seizures occurred early in the course of treatment, some seizures did occur after several weeks at fixed dose.

***Recommendations for reducing the risk of seizure:* Retrospective analysis of clinical experience gained during the development of Wellbutrin suggests that the risk of seizure may be minimized if (1) the total daily dose of Wellbutrin does *not* exceed 450 mg, (2) the daily dose is administered t.i.d., with each single dose *not* to exceed 150 mg to avoid high peak concentrations of bupropion and/or its metabolites, and (3) the rate of incrementation of dose is very gradual. Extreme caution should be used when Wellbutrin is (1) administered to patients with a history of seizure, cranial trauma, or other predisposition(s) toward seizure, or (2) prescribed with other agents (e.g., antipsychotics, other antidepressants, etc.) or treatment regimens (e.g., abrupt discontinuation of a benzodiazepine) that lower seizure threshold.**

Potential for Hepatotoxicity: In rats receiving large doses of bupropion chronically, there was an increase in incidence of hepatic hyperplastic nodules and hepatocellular hypertrophy. In dogs receiving large doses of bupropion chronically, various histologic changes were seen in the liver, and laboratory tests suggesting mild hepatocellular injury were noted. Although scattered abnormalities in liver function tests were detected in patients participating in clinical trials, there is no clinical evidence that bupropion acts as a hepatotoxin in humans.

PRECAUTIONS: General:

Agitation and Insomnia: A substantial proportion of patients treated with Wellbutrin experience some degree of increased restlessness, agitation, anxiety, and insomnia, especially shortly after initiation of treatment. In clinical studies, these symptoms were sometimes of sufficient magnitude to require treatment with sedative/hypnotic drugs. In approximately 2% of patients, symptoms were sufficiently severe to require discontinuation of Wellbutrin treatment.

Psychosis, Confusion, and Other Neuropsychiatric Phenomena: Patients treated with Wellbutrin have been reported to show a variety of neuropsychiatric signs and symptoms including delusions, hallucinations, psychotic episodes, confusion, and paranoia. Because of the uncontrolled nature of many studies, it is impossible to provide a precise estimate of the extent of risk imposed by treatment with Wellbutrin. In several cases, neuropsychiatric phenomena abated upon dose reduction and/or withdrawal of treatment.

Activation of Psychosis and/or Mania: Antidepressants can precipitate manic episodes in Bipolar Manic Depressive patients during the depressed phase of their illness and may activate latent psychosis in other susceptible patients. Wellbutrin is expected to pose similar risks.

Altered Appetite and Weight: A weight loss of greater than 5 pounds occurred in 28% of Wellbutrin patients. This incidence is approximately double that seen in comparable patients treated with tricyclics or placebo. Furthermore, while 34.5% of patients receiving tricyclic antidepressants gained weight, only 9.4% of patients treated with Wellbutrin did. Consequently, if weight loss is a major presenting sign of a patient's depressive illness, the anorectic and/or weight reducing potential of Wellbutrin should be considered.

Suicide: The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Accordingly, prescriptions for Wellbutrin should be written for the smallest number of tablets consistent with good patient management.

Use in Patients with Systemic Illness: There is no clinical experience establishing the safety of Wellbutrin in patients with a recent history of myocardial infarction or unstable heart disease. Therefore, care should be exercised if it is used in these groups.

Because bupropion HCl and its metabolites are almost completely excreted through the kidney and metabolites are likely to undergo conjugation in the liver prior to urinary excretion, treatment of patients with renal or hepatic impairment should be initiated at reduced dosage as bupropion and its metabolites may accumulate in such patients beyond concentrations expected in patients without renal or hepatic impairment. The patient should be closely monitored for possible toxic effects of elevated blood and tissue levels of drug and metabolites.

Information for Patients: Consult complete product information.

Drug Interactions: No systematic data have been collected on the consequences of the concomitant administration of Wellbutrin and other drugs.

However, animal data suggest that Wellbutrin may be an inducer of drug metabolizing enzymes. This may be of potential clinical importance because the blood levels of co-administered drugs may be altered.

Alternatively, because bupropion is extensively metabolized, the co-administration of other drugs may affect its clinical activity. In particular, care should be exercised when administering drugs known to affect hepatic drug metabolizing enzyme systems (e.g., carbamazepine, cimetidine, phenobarbital, phenytoin).

Studies in animals demonstrate that the acute toxicity of bupropion is enhanced by the MAO inhibitor phenelzine (see CONTRAINDICATIONS).

Limited clinical data suggest a higher incidence of adverse experiences in patients receiving concurrent administration of Wellbutrin and L-dopa. Administration of Wellbutrin to patients receiving L-dopa concurrently should be undertaken with caution, using small initial doses and small gradual dose increases.

Concurrent administration of Wellbutrin and agents which lower seizure threshold should be undertaken only with extreme caution (see WARNINGS). Low initial dosing and small gradual dose increases should be employed.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Lifetime carcinogenicity studies were performed in rats and mice at doses up to 300 and 150 mg/kg/day, respectively. In the rat study there was an increase in nodular proliferative lesions of the liver at doses of 100 to 300 mg/kg/day; lower doses were not tested. The question of whether or not such lesions may be precursors of neoplasms of the liver is currently unresolved. Similar liver lesions were not seen in the mouse study, and no increase in malignant tumors of the liver and other organs was seen in either study.

Bupropion produced a borderline positive response (2-3 times control mutation rate) in some strains in the Ames bacterial mutagenicity test, and a high oral dose (300, but not 100 or 200 mg/kg) produced a low incidence of chromosomal aberrations in rats. The relevance of these results in estimating the risk of human exposure to therapeutic doses is unknown.

A fertility study was performed in rats; no evidence of impairment of fertility was encountered at oral doses up to 300 mg/kg/day.

Pregnancy: ***Teratogenic Effects:*** Pregnancy Category B: Reproduction studies have been performed in rabbits and rats at doses up to 15-45 times the human daily dose and have revealed no definitive evidence of impaired fertility or harm to the fetus due to bupropion. (In rabbits, a slightly increased incidence of fetal abnormalities was seen in two studies, but there was no increase in any specific abnormality). There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery: The effect of Wellbutrin on labor and delivery in humans is unknown.

Nursing Mothers: Because of the potential for serious adverse reactions in nursing infants from Wellbutrin, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: The safety and effectiveness of Wellbutrin in individuals under 18 years old have not been established.

Use in the Elderly: Wellbutrin has not been systematically evaluated in older patients.

ADVERSE REACTIONS: (See also WARNINGS and PRECAUTIONS) Adverse events commonly encountered in patients treated with Wellbutrin are agitation, dry mouth, insomnia, headache/migraine, nausea/vomiting, constipation, and tremor.

Adverse events were sufficiently troublesome to cause discontinuation of Wellbutrin treatment in approximately ten percent of the 2400 patients and volunteers who participated in clinical trials during the product's initial development. The more common events causing discontinuation include neuropsychiatric disturbances (3.0%), primarily agitation and abnormalities in mental status; gastrointestinal disturbances (2.1%), primarily nausea and vomiting; neurological disturbances (1.7%), primarily seizures, headaches, and sleep disturbances; and dermatologic problems (1.4%), primarily rashes. It is important to note, however, that many of these events occurred at doses that exceed the recommended daily dose.

The table below is presented solely to indicate the relative frequency of adverse events reported in representative controlled clinical studies conducted to evaluate the safety and efficacy of Wellbutrin under relatively similar conditions of daily dosage (300-600 mg), setting, and duration (3-4 weeks). The figures cited cannot be used to predict precisely the incidence of untoward events in the course of usual medical practice where patient characteristics and other factors must differ from those which prevailed in the clinical trials. These incidence figures also cannot be compared with those obtained from other clinical studies involving related drug products as each group of drug trials is conducted under a different set of conditions.

Finally, it is important to emphasize that the tabulation does not reflect the relative severity and/or clinical importance of the events. A better perspective on the serious adverse events associated with the use of Wellbutrin is provided in the WARNINGS and PRECAUTIONS sections.

TREATMENT EMERGENT ADVERSE EXPERIENCE INCIDENCE IN PLACEBO-CONTROLLED CLINICAL TRIALS*
(Percent of Patients Reporting)

Adverse Experience	Wellbutrin Patients (n = 323)	Placebo Patients (n = 185)
CARDIOVASCULAR		
Cardiac Arrhythmias	5.3	4.3
Dizziness	22.3	16.2
Hypertension	4.3	1.6
Hypotension	2.5	2.2
Palpitations	3.7	2.2
Syncope	1.2	0.5
Tachycardia	10.8	8.6
DERMATOLOGIC		
Pruritus	2.2	0.0
Rash	8.0	6.5
GASTROINTESTINAL		
Anorexia	18.3	18.4
Appetite Increase	3.7	2.2
Constipation	26.0	17.3
Diarrhea	6.8	8.6
Dyspepsia	3.1	2.2
Nausea/Vomiting	22.9	18.9
Weight Gain	13.6	22.7
Weight Loss	23.2	23.2
GENITOURINARY		
Impotence	3.4	3.1
Menstrual Complaints	4.7	1.1
Urinary Frequency	2.5	2.2
Urinary Retention	1.9	2.2
MUSCULOSKELETAL		
Arthritis	3.1	2.7
NEUROLOGICAL		
Akathisia	1.5	1.1
Akinesia/Bradykinesia	8.0	8.6
Cutaneous Temperature Disturbance	1.9	1.6
Dry Mouth	27.6	18.4
Excessive Sweating	22.3	14.6
Headache/Migraine	25.7	22.2
Impaired Sleep Quality	4.0	1.6
Increased Salivary Flow	3.4	3.8
Insomnia	18.6	15.7
Muscle Spasms	1.9	3.2
Pseudoparkinsonism	1.5	1.6
Sedation	19.8	19.5
Sensory Disturbance	4.0	3.2
Tremor	21.1	7.6
NEUROPSYCHIATRIC		
Agitation	31.9	22.2
Anxiety	3.1	1.1
Confusion	8.4	4.9
Decreased Libido	3.1	1.6
Delusions	1.2	1.1
Disturbed Concentration	3.1	3.8
Euphoria	1.2	0.5
Hostility	5.6	3.8
NONSPECIFIC		
Fatigue	5.0	8.6
Fever/Chills	1.2	0.5
RESPIRATORY		
Upper Respiratory Complaints	5.0	11.4
SPECIAL SENSES		
Auditory Disturbance	5.3	3.2
Blurred Vision	14.6	10.3
Gustatory Disturbance	3.1	1.1

*Events reported by at least 1% of Wellbutrin patients are included.

Other events observed during the development of Wellbutrin: The conditions and duration of exposure to Wellbutrin varied greatly and a substantial proportion of the experience was gained in open and uncontrolled clinical settings. During this experience, numerous adverse events were reported; however, without appropriate controls, it is impossible to determine with certainty which events were or were not caused by Wellbutrin. The following enumeration is organized by organ system and describes events in terms of their relative frequency of reporting in the data base. Events of major clinical importance are also described in the WARNINGS and PRECAUTIONS sections of the labeling.

The following definitions of frequency are used: Frequent adverse events are defined as those occurring in at least 1/100 patients. Infrequent adverse events are those occurring in 1/100 to 1/1000 patients, while rare events are those occurring in less than 1/1000 patients.

Cardiovascular: Frequent was edema; infrequent were chest pain, EKG abnormalities (premature beats and nonspecific ST-T changes), and shortness of breath/dyspnea; rare were flushing, pallor, phlebitis and myocardial infarction.

Dermatologic: Frequent were nonspecific rashes; infrequent were alopecia and dry skin; rare were change in hair color, hirsutism and acne.

Endocrine: Infrequent was gynecomastia; rare were glycosuria and hormone level change.

Gastrointestinal: Infrequent were dysphagia, thirst disturbance, and liver damage/jaundice; rare were rectal complaints, colitis, G.I. bleeding, intestinal perforation and stomach ulcer.

Genitourinary: Frequent was nocturia; infrequent were vaginal irritation, testicular swelling, urinary tract infection, painful erection, and retarded ejaculation; rare were dysuria, enuresis, urinary incontinence, menopause, ovarian disorder, pelvic infection, cystitis, dyspareunia, and painful ejaculation.

Hematologic/Oncologic: Rare were lymphadenopathy, anemia and pancytopenia.

Musculoskeletal: Rare was musculoskeletal chest pain.

Neurological: (see WARNINGS) Frequent were ataxia/incoordination, seizure, myoclonus, dyskinesia, and dystonia; infrequent were mydriasis, vertigo, and dysarthria; rare were EEG abnormality, abnormal neurological exam, impaired attention, sciatica and aphasia.

Neuropsychiatric: (see PRECAUTIONS) Frequent were mania/hypomania, increased libido, hallucinations, decrease in sexual function, and depression; infrequent were memory impairment, depersonalization, psychosis, dysphoria, mood instability, paranoia, formal thought disorder, and frigidity; rare was suicidal ideation.

Oral Complaints: Frequent was stomatitis; infrequent were toothache, bruxism, gum irritation, and oral edema; rare was glossitis.

Respiratory: Infrequent were bronchitis and shortness of breath/dyspnea; rare were epistaxis, rate or rhythm disorder, pneumonia and pulmonary embolism.

Special Senses: Infrequent was visual disturbance; rare was diplopia.

Nonspecific: Frequent were flu-like symptoms; infrequent was nonspecific pain; rare were body odor, surgically related pain, infection, medication reaction and overdose.

DOSAGE AND ADMINISTRATION: General Dosing Considerations: It is particularly important to administer Wellbutrin in a manner most likely to minimize the risk of seizure (see WARNINGS). Increases in dose should not exceed 100 mg/day in a 3 day period. Gradual escalation in dosage is also important if agitation, motor restlessness, and insomnia, often seen during the initial days of treatment, are to be minimized. If necessary, these effects may be managed by temporary reduction of dose or the short-term administration of an intermediate to long-acting sedative hypnotic. A sedative hypnotic usually is not required beyond the first week of treatment. Insomnia may also be minimized by avoiding bedtime doses. If distressing, untoward effects supervene, dose escalation should be stopped.

No single dose of Wellbutrin should exceed 150 mg. Wellbutrin should be administered t.i.d., preferably with at least 6 hours between successive doses.

Usual Dosage for Adults: The usual adult dose is 300 mg/day, given t.i.d. Dosing should begin at 200 mg/day, given as 100 mg b.i.d. Based on clinical response, this dose may be increased to 300 mg/day, given as 100 mg t.i.d., no sooner than 3 days after beginning therapy (see table below).

Dosing Regimen

Treatment Day	Total Daily Dose	Tablet Strength	Number of Tablets		
			Morning	Midday	Evening
1	200 mg	100 mg	1	0	1
4	300 mg	100 mg	1	1	1

Increasing the Dosage Above 300 mg/Day: As with other antidepressants, the full antidepressant effect of Wellbutrin may not be evident until 4 weeks of treatment or longer. An increase in dosage, up to a maximum of 450 mg/day, given in divided doses of not more than 150 mg each, may be considered for patients in whom no clinical improvement is noted after several weeks of treatment at 300 mg/day. Dosing above 300 mg/day may be accomplished using the 75 or 100 mg tablets. The 100 mg tablet must be administered q.i.d. with at least 4 hours between successive doses, in order not to exceed the limit of 150 mg in a single dose. Wellbutrin should be discontinued in patients who do not demonstrate an adequate response after an appropriate period of treatment at 450 mg/day.

Elderly Patients: In general, older patients are known to metabolize drugs more slowly and to be more sensitive to the anticholinergic, sedative, and cardiovascular side effects of antidepressant drugs.

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(Continued from page A16)

ecutive Director, 103 South Adams Street, Rockville, MD 20850; 301-251-2790.

March 21–22, 18th annual conference, The New York Branch of the Orton Dyslexia Society, New York. Contact: Amy Bailin, New York Branch of the Orton Dyslexia Society, 80 Fifth Avenue, New York, NY 10011; 212-691-1930.

March 22–24, annual meeting, Association for Child Psychoanalysis, St. Louis. Contact: Charles A. Mangham, M.D., President, P.O. Box 5935, Washington, DC 20016; 202-363-7849.

March 23–26, annual meeting, American Orthopsychiatric Association, Toronto, Ontario. Contact: Herbert A. Sohn, Ph.D., Executive Director, 19 West 44th Street, Suite 1616, New York, NY 10036; 212-354-5770.

APRIL

April 3–5, 2nd International Congress on Emergency Psychiatry, Amsterdam. Contact: 2nd International Congress on Emergency Psychiatry, c/o Leids Congres Bureau, P.O. Box 16065, 2301 GB Leiden, The Netherlands; 31-71-275299.

April 4–7, annual meeting, Bulimia Anorexia Self-Help, Inc., St. Louis. Contact: Felix E.F. Larocca, M.D., President, P.O. Box 39903, St. Louis, MO 63139; 314-567-4080.

April 10–13, international conference, "Changing Mental Health Care in the Cities of Europe," Amsterdam. Contact: Congress Secretariat, QLT/CONGREX, Keizersgracht 782, 1017 EC Amsterdam, The Netherlands; 31-0-20-26-13-72.

April 11–14, annual meeting, American College of Physicians, New Orleans. Contact: John Ball, M.D., J.D., Executive Vice-President, Sixth Street at Race, Philadelphia, PA 19106; 215-351-2400.

April 15–19, annual meeting, American Society of Clinical Hypnosis, St. Louis. Contact: William F. Hoffmann, Jr., Executive Vice-President, 2250 East Devon Avenue, Suite 336, Des Plaines, IL 60018; 708-297-3317.

April 17–19, international symposium, "Eating Disorders," International Society for Adolescent Psychiatry in Association With the Eating Disorders Section of the World Psychiatric Association, Paris. Contact: Herman D. Staples, M.D., IACAPAP Coordinator for North America, 24 Green Valley Road, Wallingford, PA 19086.

April 17–21, annual meeting, American Association of Suicidology, Boston. Contact: Julie Perlman, M.S.W., Executive Officer, 2459 South Ash, Denver, CO 80222; 303-692-0985.

April 18–20, annual meeting, Society for Research in Child Development, Seattle. Contact: John W. Hagen, Executive Officer, 300 North Ingalls Boulevard, Ann Arbor, MI 48109-0406; 313-764-2443.

April 18–21, annual meeting, National Council on Alcoholism and Drug Dependence, Boston. Contact: Hamilton Beazley, President, 12 West 21st Street, 8th Floor, New York, NY 10010; 212-206-6770.

April 18–21, 9th Annual Symposium in Forensic Psychiatry, American College of Forensic Psychiatry, Newport Beach, Calif. Contact: Ed Miller, Executive Director, 26701 Quail Creek, Suite 295, Laguna Hills, CA 92656; 714-831-0236.

April 21–24, annual meeting, American Association for Counseling and Development, Reno, Nev. Contact: William W. Hunter, Acting Executive Director, 5999 Stevenson Avenue, Alexandria, VA 22304; 703-823-9800.

April 21–27, annual meeting, American Academy of Neurology, Boston. Contact: Jan W. Kolehmainen, Executive Director, 2221 University Avenue, S.E., Suite 335, Minneapolis, MN 55414; 612-623-8115.

April 26–27, conference, "Women," Cambridge Hospital and Harvard Medical School and The Stone Center at Wellesley College, Boston. Contact: Judy Reiner Platt, Cambridge Hospital, 1493 Cambridge Street, Cambridge, MA 02139; 617-864-6165.

April 30–May 5, annual meeting, American Association of Sex Educators, Counselors and Therapists, St. Louis. Contact: David G. Lister, Executive Director, 435 North Michigan Avenue, Suite 1717, Chicago, IL 60611; 312-644-0828.

MAY

May 1–4, annual meeting, American Association for the History of Medicine, Cleveland. Contact: Dr. Gerald N. Grob, chair, AAHM Program Committee, Institute for Health Policy, 30 College Avenue, Rutgers University, New Brunswick, NJ 08903; 908-932-8377.

May 3–5, Advanced Clinical Course in Pediatric Obesity, University of California, San Francisco, Center for Child and Adolescent Obesity. Contact: Laurel Mellin, Center for Child and Adolescent Obesity, Department of Family and Community Medicine, Box 0900, University of California, San Francisco, CA 94143; 415-476-1482.

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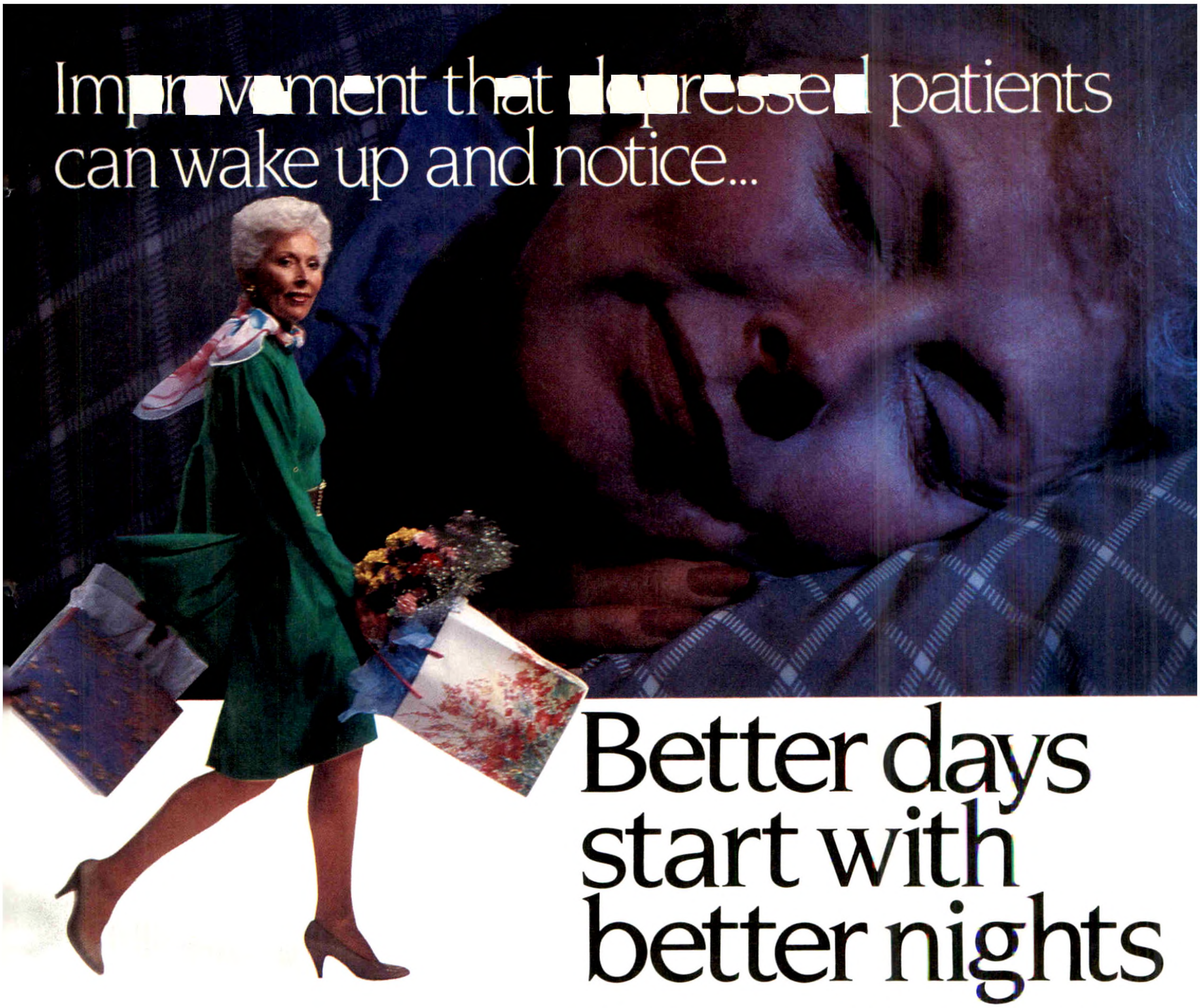

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- Sleep disturbances respond particularly well to once-a-day Sinequan® (doxepin HCl)... as it works to relieve underlying depression and anxiety.[2,3]

The possibility of drug interaction should be considered if the patient is receiving other drugs concomitantly.

Antidepressant effectiveness with the nighttime advantage

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(doxepin HCl)

150-mg,* 100-mg, 75-mg, 50-mg, 25-mg, and 10-mg CAPSULES; ORAL CONCENTRATE, 10-mg/mL, 120-mL (4-oz) bottles

***The 150-mg capsule strength is intended for maintenance therapy only and is not recommended for initiation of treatment.**

Please see brief summary of SINEQUAN® (doxepin HCl) prescribing information on next page.

ROERIG Pfizer
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References: 1. Goldberg HL: Sleep disturbance as a manifestation of depression, in *Somatic Depression: Insights for Primary Care Physicians*. Proceedings of a symposium held in Miami, Dec 4, 1978. New York, Postgraduate Medicine Communications, pp 13-18. **2.** Karacan I, Blackburn AB, Thornby JI, et al: The effect of doxepin HCl (Sinequan) on sleep patterns and clinical symptomatology of neurotic depressed patients with sleep disturbance, in *Sinequan® (doxepin HCl): A Monograph of Recent Clinical Studies*. Princeton, NJ, Excerpta Medica, 1977, pp 4-22. **3.** Goldberg HL, Finnerty RJ: The use of doxepin in the treatment of symptoms of anxiety neurosis and accompanying depression: A collaborative controlled study. *Am J Psychiatry* 1972;129(July):74-77.

SINEQUAN® (doxepin HCl)

BRIEF SUMMARY
SINEQUAN® (doxepin HCl) Capsules/Oral Concentrate

Contraindications. SINEQUAN is contraindicated in individuals who have shown hypersensitivity to the drug. Possibility of cross sensitivity with other dibenzoxepines should be kept in mind.

SINEQUAN is contraindicated in patients with glaucoma or a tendency to urinary retention. These disorders should be ruled out, particularly in older patients.

Warnings. The once-a-day dosage regimen of SINEQUAN in patients with intercurrent illness or patients taking other medications should be carefully adjusted. This is especially important in patients receiving other medications with anticholinergic effects.

Usage in Geriatrics: The use of SINEQUAN on a once-a-day dosage regimen in geriatric patients should be adjusted carefully based on the patient's condition.

Usage in Pregnancy: Reproduction studies have been performed in rats, rabbits, monkeys and dogs and there was no evidence of harm to the animal fetus. The relevance to humans is not known. Since there is no experience in pregnant women who have received this drug, safety in pregnancy has not been established. There has been a report of apnea and drowsiness occurring in a nursing infant whose mother was taking SINEQUAN.

Usage in Children: The use of SINEQUAN in children under 12 years of age is not recommended because safe conditions for its use have not been established.

Drug Interactions.

MAO Inhibitors: Serious side effects and even death have been reported following the concomitant use of certain drugs with MAO inhibitors. Therefore, MAO inhibitors should be discontinued at least two weeks prior to the cautious initiation of therapy with SINEQUAN. The exact length of time may vary and is dependent upon the particular MAO inhibitor being used, the length of time it has been administered, and the dosage involved.

Cimetidine: Cimetidine has been reported to produce clinically significant fluctuations in steady-state serum concentrations of various tricyclic antidepressants. Serious anticholinergic symptoms (i.e., severe dry mouth, urinary retention and blurred vision) have been associated with elevations in the serum levels of tricyclic antidepressant when cimetidine therapy is initiated. Additionally, higher than expected tricyclic antidepressant levels have been observed when they are begun in patients already taking cimetidine. In patients who have been reported to be well controlled on tricyclic antidepressants receiving concurrent cimetidine therapy, discontinuation of cimetidine has been reported to decrease established steady-state serum tricyclic antidepressant levels and compromise their therapeutic effects.

Alcohol: It should be borne in mind that alcohol ingestion may increase the danger inherent in any intentional or unintentional SINEQUAN overdosage. This is especially important in patients who may use alcohol excessively.

Tolazamide: A case of severe hypoglycemia has been reported in a type II diabetic patient maintained on tolazamide (1 gm/day) 11 days after the addition of doxepin (75 mg/day).

Precautions. Since drowsiness may occur with the use of this drug, patients should be warned of the possibility and cautioned against driving a car or operating dangerous machinery while taking the drug. Patients should also be cautioned that their response to alcohol may be potentiated.

Since suicide is an inherent risk in any depressed patient and may remain so until significant improvement has occurred, patients should be closely supervised during the early course of therapy. Prescriptions should be written for the smallest feasible amount.

Should increased symptoms of psychosis or shift to manic symptomatology occur, it may be necessary to reduce dosage or add a major tranquilizer to the dosage regimen.

Adverse Reactions. NOTE: Some of the adverse reactions noted below have not been specifically reported with SINEQUAN use. However, due to the close pharmacological similarities among the tricyclics, the reactions should be considered when prescribing SINEQUAN (doxepin HCl).

Anticholinergic Effects: Dry mouth, blurred vision, constipation, and urinary retention have been reported. If they do not subside with continued therapy, or become severe, it may be necessary to reduce the dosage.

Central Nervous System Effects: Drowsiness is the most commonly noticed side effect. This tends to disappear as therapy is continued. Other infrequently reported CNS side effects are confusion, disorientation, hallucinations, numbness, paresthesias, ataxia, extrapyramidal symptoms, seizures, tardive dyskinesia, and tremor.

Cardiovascular: Cardiovascular effects including hypotension, hypertension, and tachycardia have been reported occasionally.

Allergic: Skin rash, edema, photosensitization, and pruritus have occasionally occurred.

Hematologic: Eosinophilia has been reported in a few patients. There have been occasional reports of bone marrow depression manifesting as agranulocytosis, leukopenia, thrombocytopenia, and purpura.

Gastrointestinal: Nausea, vomiting, indigestion, taste disturbances, diarrhea, anorexia, and aphthous stomatitis have been reported. (See anticholinergic effects.)

Endocrine: Raised or lowered libido, testicular swelling, gynecomastia in males, enlargement of breasts and galactorrhea in the female, raising or lowering of blood sugar levels, and syndrome of inappropriate antidiuretic hormone secretion have been reported with tricyclic administration.

Other: Dizziness, tinnitus, weight gain, sweating, chills, fatigue, weakness, flushing, jaundice, alopecia, headache, exacerbation of asthma, and hyperpyrexia (in association with chlorpromazine) have been occasionally observed as adverse effects.

Withdrawal Symptoms: The possibility of development of withdrawal symptoms upon abrupt cessation of treatment after prolonged SINEQUAN administration should be borne in mind. These are not indicative of addiction and gradual withdrawal of medication should not cause these symptoms.

Dosage and Administration. For most patients with illness of mild to moderate severity, a starting daily dose of 75 mg is recommended. Dosage may subsequently be increased or decreased at appropriate intervals and according to individual response. The usual optimum dose range is 75 mg/day to 150 mg/day.

In more severely ill patients higher doses may be required with subsequent gradual increase to 300 mg/day if necessary. Additional therapeutic effect is rarely to be obtained by exceeding a dose of 300 mg/day.

In patients with very mild symptomatology or emotional symptoms accompanying organic disease, lower doses may suffice. Some of these patients have been controlled on doses as low as 25-50 mg/day.

The total daily dosage of SINEQUAN may be given on a divided or once-a-day dosage schedule. If the once-a-day schedule is employed the maximum recommended dose is 150 mg/day. This dose may be given at bedtime. **The 150 mg capsule strength is intended for maintenance therapy only and is not recommended for initiation of treatment.**

Anti-anxiety effect is apparent before the antidepressant effect. Optimal antidepressant effect may not be evident for two to three weeks.

Overdosage.

A. Signs and Symptoms

1. Mild: Drowsiness, stupor, blurred vision, excessive dryness of mouth.
2. Severe: Respiratory depression, hypotension, coma, convulsions, cardiac arrhythmias and tachycardias.

Also: urinary retention (bladder atony), decreased gastrointestinal motility (paralytic ileus), hyperthermia (or hypothermia), hypertension, dilated pupils, hyperactive reflexes.

B. Management and Treatment

1. Mild: Observation and supportive therapy is all that is usually necessary.
2. Severe: Medical management of severe SINEQUAN overdosage consists of aggressive supportive therapy. If the patient is conscious, gastric lavage, with appropriate precautions to prevent pulmonary aspiration, should be performed even though SINEQUAN is rapidly absorbed. The use of activated charcoal has been recommended, as has been continuous gastric lavage with saline for 24 hours or more. An adequate airway should be established in comatose patients and assisted ventilation used if necessary. EKG monitoring may be required for several days, since relapse after apparent recovery has been reported. Arrhythmias should be treated with the appropriate antiarrhythmic agent. It has been reported that many of the cardiovascular and CNS symptoms of tricyclic antidepressant poisoning in adults may be reversed by the slow intravenous administration of 1 mg to 3 mg of physostigmine salicylate. Because physostigmine is rapidly metabolized, the dosage should be repeated as required. Convulsions may respond to standard anticonvulsant therapy, however, barbiturates may potentiate any respiratory depression. Dialysis and forced diuresis generally are not of value in the management of overdosage due to high tissue and protein binding of SINEQUAN.

More detailed professional information available on request.

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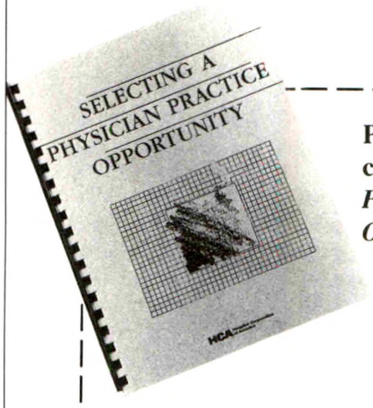

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*References supporting these statements available from MERRELL DOW PHARMACEUTICALS INC., Cincinnati, Ohio 45242.

†Norpramin does not usually inhibit normal activity, although patients should be cautioned against driving or operating machinery if drowsiness occurs (see Warnings, Precautions, and Adverse Reactions).

8-1912 (NR081) February, 1989 Printed in U.S.A.

Norpramin® 10, 25, 50, 75, 100, 150 mg

(desipramine hydrochloride tablets USP)

Norpramin®

(desipramine hydrochloride tablets USP)

BRIEF SUMMARY

CAUTION: Federal law prohibits dispensing without prescription.

INACTIVE INGREDIENTS

The following inactive ingredients are contained in all dosage strengths: acacia, calcium carbonate, corn starch, D&C Red No. 30 and D&C Yellow No. 10 (except 10 mg and 150 mg), FD&C Blue No. 1, FD&C Red No. 3, FD&C Yellow No. 6, hydrogenated soy oil, iron oxide, light mineral oil, magnesium stearate, mannitol, polyethylene glycol 8000, pregelatinized corn starch, sodium benzoate (except 150 mg), sucrose, talc, titanium dioxide, and other ingredients.

CLINICAL PHARMACOLOGY

Metabolism

The rate of metabolism of tricyclic antidepressants varies widely from individual to individual, chiefly on a genetically determined basis. In general, the elderly metabolize tricyclic antidepressants more slowly than do younger adults.

Certain drugs, particularly the psychostimulants and the phenothiazines, increase plasma levels of concomitantly administered tricyclic antidepressants through competition for the same metabolic enzyme systems. Other substances, particularly barbiturates and alcohol, induce liver enzyme activity and thereby reduce tricyclic antidepressant plasma levels. Similar effects have been reported with tobacco smoke.

Additional information on metabolism appears in Full Prescribing Information.

CONTRAINDICATIONS

Desipramine hydrochloride should not be given in conjunction with, or within 2 weeks of, treatment with an MAO inhibitor drug; hyperpyretic crises, severe convulsions, and death have occurred in patients taking MAO inhibitors and tricyclic antidepressants. When Norpramin (desipramine hydrochloride) is substituted for an MAO inhibitor, at least 2 weeks should elapse between treatments. Norpramin should then be started cautiously and should be increased gradually.

The drug is contraindicated in the acute recovery period following myocardial infarction. It should not be used in those who have shown prior hypersensitivity to the drug. Cross sensitivity between this and other dibenzazepines is a possibility.

WARNINGS

1. Extreme caution should be used when this drug is given in the following situations:
   a. In patients with cardiovascular disease, because of the possibility of conduction defects, arrhythmias, tachycardias, strokes, and acute myocardial infarction.
   b. In patients with a history of urinary retention or glaucoma, because of the anticholinergic properties of the drug.
   c. In patients with thyroid disease or those taking thyroid medication, because of the possibility of cardiovascular toxicity, including arrhythmias.
   d. In patients with a history of seizure disorder, because this drug has been shown to lower the seizure threshold.
2. This drug is capable of blocking the antihypertensive effect of guanethidine and similarly acting compounds.
3. **USE IN PREGNANCY**
   Safe use of desipramine hydrochloride during pregnancy and lactation has not been established; therefore, if it is to be given to pregnant patients, nursing mothers, or women of childbearing potential, the possible benefits must be weighed against the possible hazards to mother and child. Animal reproductive studies have been inconclusive.
4. **USE IN CHILDREN**
   Norpramin (desipramine hydrochloride) is not recommended for use in children since safety and effectiveness in the pediatric age group have not been established. (See ADVERSE REACTIONS, Cardiovascular.)
5. The patient should be cautioned that this drug may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery.
6. In patients who may use alcohol excessively, it should be borne in mind that the potentiation may increase the danger inherent in any suicide attempt or overdosage.

PRECAUTIONS

1. It is important that this drug be dispensed in the least possible quantities to depressed outpatients, since suicide has been accomplished with this class of drug. Ordinary prudence requires that children not have access to this drug or to potent drugs of any kind; if possible, this drug should be dispensed in containers with child-resistant safety closures. Storage of this drug in the home must be supervised responsibly.
2. If serious adverse effects occur, dosage should be reduced or treatment should be altered.
3. Norpramin (desipramine hydrochloride) therapy in patients with manic-depressive illness may induce a hypomanic state after the depressive phase terminates.
4. The drug may cause exacerbation of psychosis in schizophrenic patients.
5. Close supervision and careful adjustment of dosage are required when this drug is given concomitantly with anticholinergic or sympathomimetic drugs.
6. Patients should be warned that while taking this drug their response to alcoholic beverages may be exaggerated.
7. Clinical experience in the concurrent administration of ECT and antidepressant drugs is limited. Thus, if such treatment is essential, the possibility of increased risk relative to benefits should be considered.
8. If Norpramin (desipramine hydrochloride) is to be combined with other psychotropic agents such as tranquilizers or sedative/hypnotics, careful consideration should be given to the pharmacology of the agents employed since the sedative effects of Norpramin and benzodiazepines (e.g., chlordiazepoxide or diazepam) are additive. Both the sedative and anticholinergic effects of the major tranquilizers are also additive to those of Norpramin.
9. Concurrent administration of cimetidine and tricyclic antidepressants can produce clinically significant increases in the plasma levels of the tricyclic antidepressants. Conversely, decreases in plasma levels of the tricyclic antidepressants have been reported upon discontinuation of cimetidine which may result in the loss of the therapeutic efficacy of the tricyclic antidepressant.
10. This drug should be discontinued as soon as possible prior to elective surgery because of the possible cardiovascular effects. Hypertensive episodes have been observed during surgery in patients taking desipramine hydrochloride.
11. Both elevation and lowering of blood sugar levels have been reported.
12. Leukocyte and differential counts should be performed in any patient who develops fever and sore throat during therapy; the drug should be discontinued if there is evidence of pathologic neutrophil depression.

ADVERSE REACTIONS

Note: Included in the following listing are a few adverse reactions that have not been reported with this specific drug. However, the pharmacologic similarities among the tricyclic antidepressant drugs require that each of the reactions be considered when Norpramin (desipramine hydrochloride) is given.

Cardiovascular: hypotension, hypertension, tachycardia, palpitation, arrhythmias, heart block, myocardial infarction, stroke. There has been a report of an "acute collapse" and "sudden death" in an eight-year old (18 kg) male, treated for two years for hyperactivity. (See WARNINGS, Use in Children.)

Psychiatric: confusional states (especially in the elderly) with hallucinations, disorientation, delusions; anxiety, restlessness, agitation; insomnia and nightmares; hypomania; exacerbation of psychosis.

Neurologic: numbness, tingling, paresthesias of extremities; incoordination, ataxia, tremors; peripheral neuropathy; extrapyramidal symptoms; seizures; alteration in EEG patterns; tinnitus.

Anticholinergic: dry mouth, and rarely associated sublingual adenitis; blurred vision, disturbance of accommodation, mydriasis, increased intraocular pressure; constipation, paralytic ileus; urinary retention, delayed micturition, dilatation of urinary tract.

Allergic: skin rash, petechiae, urticaria, itching, photosensitization (avoid excessive exposure to sunlight), edema (of face and tongue or general), drug fever, cross sensitivity with other tricyclic drugs.

Hematologic: bone marrow depressions including agranulocytosis, eosinophilia, purpura, thrombocytopenia.

Gastrointestinal: anorexia, nausea and vomiting, epigastric distress, peculiar taste, abdominal cramps, diarrhea, stomatitis, black tongue.

Endocrine: gynecomastia in the male, breast enlargement and galactorrhea in the female; increased or decreased libido, impotence, painful ejaculation, testicular swelling; elevation or depression of blood sugar levels; syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Other: jaundice (simulating obstructive), altered liver function; weight gain or loss; perspiration, flushing; urinary frequency, nocturia; parotid swelling; drowsiness, dizziness, weakness and fatigue, headache; alopecia.

Withdrawal Symptoms: Though not indicative of addiction, abrupt cessation of treatment after prolonged therapy may produce nausea, headache, and malaise.

OVERDOSAGE

There is no specific antidote for desipramine, nor are there specific phenomena of diagnostic value characterizing poisoning by the drug.

Within an hour of ingestion the patient may become agitated or stuporous and then comatose. Hypotension, shock, and renal shutdown may ensue. Grand mal seizures, both early and late after ingestion, have been reported. Hyperactive reflexes, hyperpyrexia, muscle rigidity, vomiting, and ECG evidence of impaired conduction may occur. Serious disturbances of cardiac rate, rhythm, and output can occur. The precepts of early evacuation of the ingested material and subsequent support of respiration (airway and movement), circulation, and renal output apply.

The principles of management of coma and shock by means of the mechanical respirator, cardiac pacemaker, monitoring of central venous pressure, and regulation of fluid and acid-base balance are well known in most medical centers and are not further discussed here.

Because CNS involvement, respiratory depression, and cardiac arrhythmia can occur suddenly, hospitalization and close observation are generally advisable, even when the amount ingested is thought to be small or the initial degree of intoxication appears slight or moderate. Most patients with ECG abnormalities should have continuous cardiac monitoring for at least 72 hours and be closely observed until well after cardiac status has returned to normal; relapses may occur after apparent recovery.

The slow intravenous administration of physostigmine salicylate has been reported to reverse most of the anticholinergic cardiovascular and CNS effects of overdose with tricyclic antidepressants. In adults, 1 to 3 mg has been reported to be effective. In children, the dose should be started with 0.5 mg and repeated at 5-minute intervals to determine the minimum effective dose; no more than 2 mg should be given. Because of the short duration of action of physostigmine, the effective dose should be repeated at 30-minute to 60-minute intervals, as necessary. Rapid injection should be avoided to reduce the possibility of physostigmine-induced convulsions.

Other possible therapeutic considerations include:

(a) Dialysis: Desipramine is found in low concentration in the serum, even after a massive oral dose. In vitro experiments in which blood bank blood was used indicate that it is very poorly dialyzed. Because of indications that the drug is secreted in gastric juice, constant gastric lavage has been suggested.

(b) Pharmacologic treatment of shock: Since desipramine potentiates the action of such vasopressor agents as levarterenol and metaraminol, they should be used only with caution.

(c) Pharmacologic control of seizures: Intravenous barbiturates are the treatment of choice for the control of grand mal seizures. One may, alternatively, consider the parenteral use of diphenylhydantoin, which has less central depressant effect but also has an effect on heart rhythm that has not yet been fully defined.

(d) Pharmacologic control of cardiac function: Severe disturbances of cardiac rate, rhythm, and output are probably the initiating events in shock. Intravascular volume must be maintained by i.v. fluids. Digitalization should be carried out early in view of the fact that a positive inotropic effect can be achieved without increase in cardiac work. Many of the cardiodynamic effects of digitalis are the exact opposite of those of massive doses of desipramine (animal studies).

Product Information as of January, 1989 Y398D

MERRELL DOW PHARMACEUTICALS INC.
Cincinnati, Ohio 45215, U.S.A.
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THE AMERICAN JOURNAL OF PSYCHIATRY

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Ethical as well as legal considerations require careful attention to the protection of a patient's anonymity in case reports and elsewhere. Identifying information such as names, initials, hospital numbers, and dates must be avoided. In addition, authors should disguise identifying information when discussing the characteristics and personal history of patients.

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All papers are reviewed to determine the originality, validity, and importance of content and conclusions. In addition to the regular review process, peer review for statistical content may be required for some manuscripts. This will be determined by the *Journal*'s Statistical Editors. Authors will be sent reviewer comments that are judged to be useful to them. All reviewers remain anonymous. Once the Editor has made a final decision on a paper, the authors of that paper will be informed.

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The original manuscript and four copies should be submitted to John C. Nemiah, M.D., Editor, *American Journal of Psychiatry*, 1400 K St., N.W., Washington, DC 20005. All correspondence will be sent to the first-named author unless otherwise specified. Papers should be accompanied by a cover letter indicating that the paper is intended for publication and specifying for which section of the *Journal* it is being submitted (i.e., Special Article, Regular Article, or Clinical and Research Report); papers will only be reviewed after such a statement has been received from the author.

Authors will be notified of the receipt of their paper and the number assigned to it. **This number must be included in all further correspondence.** It is imperative that the corresponding author of submitted papers notify the *Journal* of changes of address. Because of escalating postage costs, no manuscripts submitted to the *Journal* will be returned to authors except upon special request. Authors must make this request in their original submission letter and include a self-addressed, postage-paid envelope.

Single Case Reports

Single case reports except for detailed longitudinal studies should be submitted as Letters to the Editor. All single case reports will be peer reviewed. Reports of successfully treated patients must include data on the number of patients treated unsuccessfully by the same method, with an indication of the temporal order of the successes and failures.

Annual Meeting Papers

Authors may submit their papers before the annual meeting, but such papers cannot be published until after the meeting. All papers must be accompanied by a statement that they are in final form. These papers are subject to the same peer review as other papers and must conform to the requirements for one of the types of articles specified in the next section.

TYPES OF ARTICLES

Special Articles

These are usually overview articles that bring together important information on a topic of general interest to psychiatry. Authors who have ideas for such articles are advised to check with the Editorial Office to ensure that a similar work has not already been submitted. Special Articles may not exceed 7,500 words (no more than 25 double-spaced pages—including an abstract of no more than 100 words, tables, and figures) and may not include more than 100 references.

Regular Articles

Regular Articles are original communications of scientific excellence in psychiatric medicine and advances in clinical research. Regular Articles contain no more than 3,800 words, including an abstract of no more than 100 words, references, tables, and figures. A table or figure that fills one-half of a vertical manuscript page equals 100 words of text; one that fills one-half of a horizontal page equals 150 words. Articles that exceed 3,800 words will be returned unreviewed to the authors.

Clinical and Research Reports

Clinical and Research Reports may contain no more than one table and a maximum of 10 references; figures may not be used. Papers may contain a **maximum** of 1,300 words, including an abstract of no more than 40 words, references, and an optional table (estimate 15 words per reference, 100 words for a double-spaced table that fills one-half of a vertical page, and 150 words for a double-spaced table that fills one-half of a horizontal page). These articles present 1) new research findings, 2) data from pilot studies, 3) worthwhile replication studies, and 4) clinical studies involving a number of patients. Essays, program descriptions, literature reviews, and single case reports do not meet the criteria for this section. Submissions that exceed 1,300 words or contain figures will be returned to the author.

Other Sections

Letters to the Editor. Brief letters (maximum of 500 words and 5 references; no tables or figures) will be considered if they include the notation "for publication." Letters critical of an article published in the *Journal* will automatically be sent to the authors for reply. Because of space limitations not all letters can be printed. The *Journal* will notify authors about the disposition of their letters but does not return those that are not published. A letter must be signed by all of its authors. All letters will be edited; edited letters will not be sent to authors for approval. Letters must be typed **double-spaced** throughout on 8½×11 inch paper; three copies are required. Letters that do not meet these specifications will be returned for revision. Reprints are not available. **Single case reports except for detailed longitudinal studies should be submitted as Letters to the Editor. Case reports submitted as Letters to the Editor will be peer reviewed.**

Book Forum. Books for review may be sent to the Book Forum Editor, Nancy C. Andreasen, M.D., Ph.D., University of Iowa College of Medicine, 500 Newton Rd., Iowa City, IA 52242. Book reviews are usually solicited by the Book Forum Editor. Authors interested in reviewing a particular book should communicate directly with Dr. Andreasen. Reprints of reviews are not available.

TYPING AND ARRANGING THE PAPER

All parts of the manuscript, including case reports, quotations, references, and tables, must be **double-spaced** throughout. Manuscripts must be typed in upper- and lowercase on one side only of 8½×11 inch **nonerasable** bond paper. All four margins must be 1½ inches. The manuscript should be arranged in the following order, with each item beginning a new page: 1) title page, 2) abstract, 3) text, 4) references, and 5) tables and/or figures. All pages must be numbered.

STYLE SPECIFICATIONS

Title Page

Title. The title should be informative and as brief as possible. Two-part titles should be avoided.

By-line. Authors listed in the by-line should be limited to principal researchers and/or writers; collaborators may be acknowledged in a footnote. Authors' first names are preferred to initials. Degrees should be included after each author's name.

Previous presentation. If the paper has been presented at a meeting, please give the name of the meeting, the place, and the date.

Location of work and address for reprints. Provide the department, institution, city, and state **where the work was done.** Include a full address for the author who is to receive reprint requests.

Acknowledgments. Grant support should be acknowledged in a separate paragraph and should include the full name of the granting agency and grant number. The *Journal* does not allow acknowledgment of persons involved with the preparation or typing of manuscripts. Acknowledgment of individuals involved with the scientific content of the work should not exceed four typed lines. Drug company support of any kind must be acknowledged.

Abstract

The abstract is a single paragraph no longer than 250 words for Special Articles and Regular Articles and no longer than 60 words for Clinical and Research Reports.

Text

Authors should use the active voice and first person; headings and subheadings should be inserted at reasonable intervals. Footnotes to text may not be used, and summaries are usually unnecessary.

Research design and statistics. The following information regarding research design should be included: 1) a clearly stated hypothesis, 2) the names of the statistical tests used, 3) whether tests were one- or two-tailed, and 4) what test was used for each set of data. Reporting of standard deviations, rather than standard errors of the mean, is required. Statistical tests that are not well known should be referenced. **All** significant and important nonsignificant results must include the test value, degree(s) of freedom, and probability. For example, "The analysis of variance indicated that those who abstained from coffee had significantly higher course grades than those who did not abstain ($F=4.32$, $df=3, 17$, $p<0.05$)." Reviewers will evaluate the appropriateness of the analyses.

Abbreviations. Spell out all abbreviations (other than those for units of measure) the first time they are used. Idiosyncratic abbreviations should not be used.

Drugs. Generic rather than trade names of drugs should be used. Trade or manufacturers' names are used only if the drug or equipment is experimental or unavailable in this country or if such information is crucial to the evaluation of the results or replication of the study.

References

References are numbered and listed by their order of appearance in text; the text citation is followed by the appropriate reference number in parentheses. Do **not** arrange the list alphabetically. References in tables and figures are numbered as though the tables and figures were part of the text.

References should be restricted to closely pertinent material. **Accuracy of citation is the author's responsibility.** References should conform exactly to the original spelling, accents, punctuation, etc. Authors should be sure that all references listed have been cited in text.

Personal communications, unpublished manuscripts, manuscripts submitted but not yet accepted, and similar unpublished items should not appear in the reference list. Such citations may be noted in text. It is the author's responsibility to obtain permission to refer to another individual's unpublished observations. Manuscripts that are actually "in press" may be cited as such in the reference list; the name of the journal or publisher and location must be included.

Type references in the style shown below, **double-spaced throughout.** List up to three authors; designate one or more authors past the third as "et al." Abbreviations of journal names should conform to the style used in *Index Medicus*; journals not indexed there should not be abbreviated.

1. Noyes R Jr, DuPont RL Jr, Pecknold JC, et al: Alprazolam in panic disorder and agoraphobia, results from a multicenter trial, II: patient acceptance, side effects, and safety. Arch Gen Psychiatry 1988; 45:423–428
2. Kaplan HI, Sadock BJ (eds): Comprehensive Textbook of Psychiatry, 4th ed, vol 2. Baltimore, Williams & Wilkins, 1985
3. Fyer AJ, Manuzza S, Endicott J: Differential diagnosis and assessments of anxiety: recent developments, in Psychopharmacology: The Third Generation of Progress. Edited by Meltzer HY. New York, Raven Press, 1987

TABLES AND FIGURES

The *Journal* does not publish tables or figures that have been submitted elsewhere or previously published. Tables and figures that duplicate 1) material contained in text or 2) each other will not be used. Authors will be asked to delete tables and figures that contain data which could be given succinctly in text. Each table and figure should be understandable without reference to the text; a descriptive, concise title should be included and units of measurement should be specified. Consult recent issues of the *Journal* for format. A table or figure that fills one-half of a vertical manuscript page equals 100 words of text; one that fills one-half of a horizontal page equals 150 words. **A copy of each table and figure must be included with each copy of the manuscript.**

Tables

Tables should be double-spaced, no wider than 120 typewriter characters, including spaces, and no longer than 70 lines. Values expressed in the same unit of measurement should read down, not across; when percentages are given, the appropriate numbers must also be given.

Figures

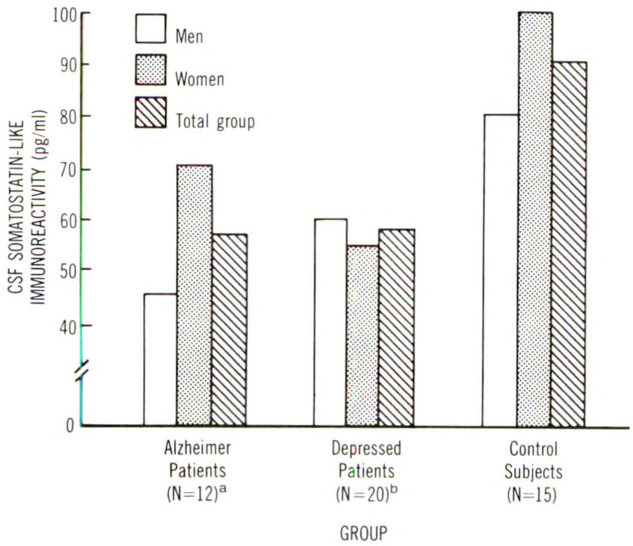
Figures are considered as text and are subject to revision by the authors upon recommendation of the Editors. Figures should, however, be professionally prepared. Glossy or other camera-ready prints should accompany the submitted manuscript. Computer-generated figures that do not meet quality printing standards will be returned for revision. The first author's name, the title of the paper, the figure number, and the top of the figure should be noted on a label affixed to the back of each figure. All figure titles and footnotes should be typed and sent together on a separate page.

The *Journal* does publish color illustrations. However, the cost to publish them, including reprint charges, will be the responsibility of the authors. An estimate of the cost will be provided to the authors at the time of first decision.

Format. Figures are visual expressions of data trends or relationships. Figures that represent numerical data which could be expressed more succinctly or clearly in tabular form should be converted to tables. Line graphs should show change in continuous variables; comparisons of like values in different groups should be presented as bar graphs. Graphs containing stacked bars are unacceptable; the different segments of each bar should be presented side by side.

Lettering. Figure type should be sans serif and should be 7 points or larger after the figure is reduced; most figures taking up the width of a vertical manuscript page are reduced to a width of 19.5 picas (3¼ inches), and those requiring a horizontal manuscript page are usually reduced to 40.5 picas (6¾ inches). When space on the horizontal axis is insuffi-

FIGURE 1. Mean CSF Somatostatin Levels of Patients With Alzheimer's Disease, Older Depressed Patients, and Age-Matched Control Subjects



[a] Significant difference between men and women ($t=1.81$, $df=10$, $p<0.05$) and between the total Alzheimer's disease group and the total control group ($t=2.49$, $df=25$, $p<0.01$).

[b] Significant difference between the total depressed group and the total control group ($t=2.75$, $df=33$, $p<0.005$).

cient, headings may be placed diagonally on the axis. Main headings should consist of upper-case letters only, subheadings of upper- and lower-case, and other type (e.g., keys, flow chart segments) of lower-case with only an initial upper-case letter. All parenthetical material should be lower-case. Do not use idiosyncratic abbreviations.

Other. The following are additional specific requirements. Please refer to the example given above.

1. Do not use solid black shading; rather, include outlined white among shadings.
2. The heading for the vertical axis of a graph should run vertically along the axis, not horizontally at the top or bottom. Headings for the horizontal axis should appear below that axis, not at the top of the graph.
3. Error bars should not be used.
4. Do not extend the vertical or horizontal axis of a graph beyond the point needed for the data shown.
5. The vertical axis should generally begin at zero; to save space, a double slash may take the place of an unused portion of the vertical axis.
6. In a graph comparing different groups of subjects, the number of subjects in each group should appear with the name of the group—in the key, in the headings below the horizontal axis, or in the title.
7. To save space, related figures that have the same vertical or horizontal axis should be combined. Headings identifying the segments of the combined figure should appear in the upper lefthand corners of the individual segments (in lower-case type with an initial upper-case letter).
8. The key should appear within or above the figure but should not be wider than the figure itself. Avoid placing other type (e.g., number of subjects, statistical values) within the axes of a graph.
9. Footnotes (including p values) should be cited with superscript letters in the title or body of the figure and should be listed in the order in which they are cited in the figure.

PROCESSING OF ACCEPTED MANUSCRIPTS

Manuscripts are accepted with the understanding that the Editor and the editorial staff have the right to make revisions aimed at greater conciseness, clarity, and conformity with *Journal* style. Accepted papers will be edited and sent to the first-named (or corresponding) author for corrections and answers to editorial queries. No proofs are sent to authors. Authors who will be away from their offices for a long period or who change address after notification of acceptance should inform the *Journal* staff.

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is the first highly specific,
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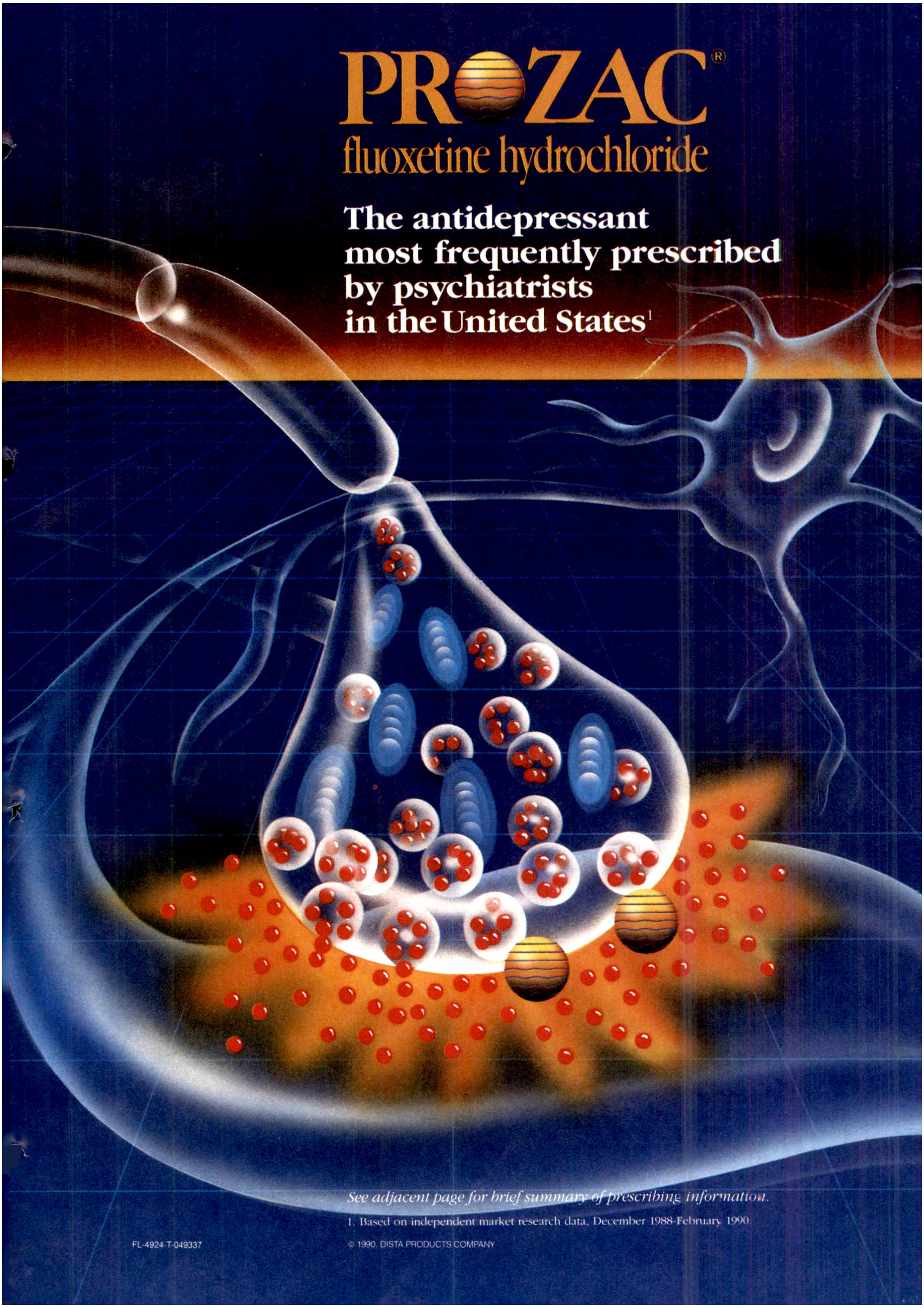
PROZAC®
fluoxetine hydrochloride
The antidepressant most frequently prescribed by psychiatrists in the United States[1]

See adjacent page for brief summary of prescribing information.

1. Based on independent market research data, December 1988-February 1990.

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Prozac® (fluoxetine hydrochloride)

Brief Summary.
Consult the package insert for complete information.

Indication: For the treatment of depression.

Contraindication: Known hypersensitivity to Prozac.

Warnings: *Monoamine Oxidase Inhibitors* — The combined use of fluoxetine and MAO inhibitors should be avoided. At least 14 days should elapse between discontinuation of an MAO inhibitor and initiation of treatment with fluoxetine.

Because of the long half-lives of fluoxetine and its active metabolite, at least five weeks (approximately five half-lives of norfluoxetine) should elapse between discontinuation of fluoxetine and initiation of an MAOI. Serious events, including death, have been reported to occur following the initiation of an MAOI shortly after discontinuation of fluoxetine.

Rash and Possibly Allergic Events — Approximately 4% of 5,600 fluoxetine patients developed a rash and/or urticaria in premarketing testing. Almost a third of these discontinued therapy because of rash and/or associated systemic signs or symptoms. Reported in association with rash were fever, leukocytosis, arthralgias, edema, carpal tunnel syndrome, respiratory distress, lymphadenopathy, proteinuria, and mild transaminase elevation. Most patients improved promptly upon discontinuation of fluoxetine and/or adjunctive treatment with antihistamines or steroids, and all were reported to recover completely.

Of two patients who developed a serious cutaneous systemic illness during premarketing clinical trials, one was considered to have a leukocytoclastic vasculitis, and the other, a severe desquamating syndrome considered variously to be a vasculitis or erythema multiforme. Other patients have had systemic syndromes suggestive of serum sickness.

Since the introduction of Prozac, systemic events possibly related to vasculitis have developed in patients with rash. Although these events are rare, they may be serious, involving the lung, kidney, or liver. Death has been reported to occur in association with these systemic events.

Anaphylactoid events, including bronchospasm, angioedema, and urticaria alone and in combination, have been reported.

Pulmonary events, including inflammatory processes of varying histopathology and/or fibrosis, have been reported rarely. These events have occurred with dyspnea as the only preceding symptom.

Whether these systemic events and rash have a common underlying cause or represent immunologic responses is not known. Upon the appearance of rash or of other possibly allergic phenomena for which an alternative etiology cannot be identified, Prozac should be discontinued.

Precautions: *General* — Anxiety, Nervousness, and Insomnia — Reported by 10% to 15% of patients, 5% of whom discontinued fluoxetine.

Altered Appetite and Weight — Significant weight loss, especially in underweight patients, may be an undesirable result of treatment.

Approximately 9% of fluoxetine patients experienced anorexia in controlled clinical trials, an incidence approximately sixfold that seen with placebo. A weight loss >5% of body weight occurred in 13% of fluoxetine patients compared with 4% in those on placebo and 3% in those on tricyclics. However, only rarely did fluoxetine patients discontinue treatment because of weight loss.

Activation of Mania/Hypomania — Hypomania or mania occurred in approximately 1% of fluoxetine patients in premarketing testing.

Seizures — Twelve of 6,000 patients (0.2%) experienced convulsions (or, possibly, seizures). Prozac should be introduced with care in patients with a history of seizures.

Suicide — Close supervision of high-risk patients should accompany initial therapy. Prescriptions of Prozac should be written for the smallest quantity of capsules consistent with good patient management to reduce the risk of overdose.

The Long Elimination Half-Lives of Fluoxetine and Its Metabolites — Because of the long elimination half-lives of the parent drug (two to three days) and its major active metabolite (seven to nine days), changes in dose will not be fully reflected in plasma for several weeks, affecting both strategies for titration to final dose and withdrawal from treatment.

Use in Patients With Concomitant Illness — Caution is advisable in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

Fluoxetine has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. ECGs of 312 patients who received Prozac in double-blind trials were retrospectively evaluated; no conduction abnormalities that resulted in heart block were observed. The mean heart rate was reduced by approximately three beats/min.

In subjects with cirrhosis, the clearances of fluoxetine and its active metabolite were decreased. A lower or less frequent dose should be used in patients with cirrhosis.

Fluoxetine should be used with caution in patients with severe renal impairment.In patients with diabetes, Prozac may alter glycemic control. Hypoglycemia has occurred during therapy with Prozac, and hyperglycemia has developed following discontinuation. Insulin and/or oral hypoglycemic dosage may need to be adjusted when fluoxetine therapy is instituted or discontinued.

Interference With Cognitive and Motor Performance — Any psychoactive drug may impair judgment, thinking or motor skills, and patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that the drug does not affect them adversely.

Information for Patients — Physicians should advise their patients to notify them if they:

- are taking or plan to take any prescription or over-the-counter drugs or alcohol
- become pregnant or intend to become pregnant during therapy
- are breast feeding an infant
- develop a rash or hives

Drug Interactions — Tryptophan — Five patients receiving tryptophan experienced adverse reactions, including agitation, restlessness, and gastrointestinal distress.

Monoamine Oxidase Inhibitors — *See* Warnings.

Other Antidepressants — There have been greater than twofold increases of previously stable plasma levels of other antidepressants when Prozac has been administered in combination with these agents.

Lithium — There have been reports of both increased and decreased lithium levels and lithium toxicity. Lithium levels should be monitored.

Diazepam Clearance — The half-life of diazepam may be prolonged in some patients.

Drugs Tightly Bound to Plasma Proteins — Because fluoxetine is tightly bound to plasma protein, the concurrent administration of fluoxetine and another tightly bound drug may cause a shift in plasma concentrations potentially resulting in an adverse effect. Adverse effects may also result from displacement of protein-bound fluoxetine by other tightly bound drugs.

CNS-Active Drugs — Caution is advised if the concomitant administration of Prozac and such drugs is required.

Electroconvulsive Therapy — There have been rare reports of prolonged seizures in patients on fluoxetine receiving ECT treatment.

Carcinogenesis, Mutagenesis, Impairment of Fertility — There is no evidence of carcinogenicity, mutagenicity, or impairment of fertility with Prozac.

The dietary administration of fluoxetine to rats and mice for two years at doses approximately 7.5 and 9.0 times the maximum human dose (80 mg) respectively revealed no evidence of carcinogenicity.

Fluoxetine and norfluoxetine have been shown to have no genotoxic effects based on the following assays: bacterial mutation assay, DNA repair assay in cultured rat hepatocytes, mouse lymphoma assay, and in vivo sister chromatid exchange assay in Chinese hamster bone marrow cells.

Two fertility studies in rats at doses approximately five and nine times the maximum human dose (80 mg) respectively revealed no adverse effects on fertility. A slight decrease in neonatal survival was noted, probably associated with depressed maternal food consumption and suppressed weight gain.

Pregnancy — Teratogenic Effects — Pregnancy Category B — Reproduction studies in rats and rabbits at doses nine and 11 times the maximum human dose (80 mg) respectively revealed no evidence of harm to the fetus. Although there have been no adequate and well-controlled studies in pregnant women, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery — The effect of Prozac on labor and delivery in humans is unknown.

Nursing Mothers — Because Prozac is known to be excreted in human milk, caution should be exercised when Prozac is administered to a nursing woman.

Usage in Children — Safety and effectiveness in children have not been established.

Usage in the Elderly — In clinical studies of several hundred elderly patients, no unusual adverse age-related phenomena were identified. However, these data are insufficient to rule out possible age-related differences during chronic use, particularly in elderly patients with concomitant systemic illnesses or those receiving concomitant drugs.

Hyponatremia — Hyponatremia (some cases with serum Na <110 mmol/L) has been reported, which appeared to be reversible on drug discontinuation. Some cases were possibly due to SIADH, and the majority have been in older patients and those taking diuretics or otherwise volume depleted.

Platelet Function — There have been rare reports of altered platelet function and/or abnormal results from laboratory studies in patients taking fluoxetine. While there have been reports of abnormal bleeding in several patients taking fluoxetine, it is unclear whether fluoxetine had a causative role.

Adverse Reactions: *Commonly Observed* — Nervous system complaints, including anxiety, nervousness, and insomnia; drowsiness and fatigue or asthenia; tremor; sweating; gastrointestinal complaints, including anorexia, nausea, and diarrhea; and dizziness or lightheadedness.

Associated With Discontinuation of Treatment — Fifteen percent of 4,000 clinical trial patients discontinued fluoxetine due to an adverse event. The more common events included: psychiatric (5.3%), primarily nervousness, anxiety, and insomnia; digestive (3.0%), primarily nausea; nervous system (1.6%), primarily dizziness; body as a whole (1.5%), primarily asthenia and headache; and skin (1.4%), primarily rash and pruritus.

Incidence in Controlled Clinical Trials — The accompanying table enumerates adverse events that occurred at a frequency of ≥ 1% in controlled trials.

TREATMENT-EMERGENT ADVERSE EXPERIENCE INCIDENCE
IN PLACEBO-CONTROLLED CLINICAL TRIALS

Body System/ Adverse Event*	Percentage of Patients Reporting Event: Prozac (N = 1,730)	Percentage of Patients Reporting Event: Placebo (N = 799)
Nervous		
Headache	20.3	15.5
Nervousness	14.9	8.5
Insomnia	13.8	7.1
Drowsiness	11.6	6.3
Anxiety	9.4	5.5
Tremor	7.9	2.4
Dizziness	5.7	3.3
Fatigue	4.2	1.1
Sedated	1.9	1.3
Sensation disturbance	1.7	2.0
Libido, decreased	1.6	—
Light-headedness	1.6	—
Concentration, decreased	1.5	—
Digestive		
Nausea	21.1	10.1
Diarrhea	12.3	7.0
Mouth dryness	9.5	6.0
Anorexia	8.7	1.5
Dyspepsia	6.4	4.3
Constipation	4.5	3.3
Pain, abdominal	3.4	2.9
Vomiting	2.4	1.3
Taste change	1.8	—
Flatulence	1.6	1.1
Gastroenteritis	1.0	1.4
Skin and Appendages		
Sweating, excessive	8.4	3.8
Rash	2.7	1.8
Pruritus	2.4	1.4
Body as a Whole		
Asthenia	4.4	1.9
Infection, viral	3.4	3.1
Pain, limb	1.6	1.1
Fever	1.4	—
Pain, chest	1.3	1.1
Allergy	1.2	1.1
Influenza	1.2	1.5
Respiratory		
Upper respiratory infection	7.6	6.0
Flu-like syndrome	2.8	1.9
Pharyngitis	2.7	1.3
Nasal congestion	2.6	2.3
Headache, sinus	2.3	1.8
Sinusitis	2.1	2.0
Cough	1.6	1.6
Dyspnea	1.4	—
Cardiovascular		
Hot flushes	1.8	1.0
Palpitations	1.3	1.4
Musculoskeletal		
Pain, back	2.0	2.4
Pain, joint	1.2	1.1
Pain, muscle	1.2	1.0
Urogenital		
Menstruation, painful	1.9	1.4
Sexual dysfunction	1.9	—
Frequent micturition	1.6	—
Urinary tract infection	1.2	—
Special Senses		
Vision disturbance	2.8	1.8

*Events reported by ≥1% of fluoxetine patients are included.
— Incidence <1%

Other Events Observed During Premarketing Evaluation in 5,600 Fluoxetine Patients — Frequent adverse events are defined as those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1,000 patients; rare events are those occurring in less than 1/1,000 patients.

Body as a Whole — *Frequent:* chills; *Infrequent:* chills and fever, cyst, face edema, hangover effect, jaw pain, malaise, neck pain, neck rigidity, and pelvic pain; *Rare:* abdomen enlarged, cellulitis, hydrocephalus, hypothermia, LE syndrome, moniliasis, and serum sickness.

Cardiovascular System — *Infrequent:* angina pectoris, arrhythmia, hemorrhage, hypertension, hypotension, migraine, postural hypotension, syncope, and tachycardia; *Rare:* AV block first-degree, bradycardia, bundle-branch block, cerebral ischemia, myocardial infarct, thrombophlebitis, vascular headache, and ventricular arrhythmia.

Digestive System — *Frequent:* increased appetite; *Infrequent:* aphthous stomatitis, dysphagia, eructation, esophagitis, gastritis, gingivitis, glossitis, liver function tests abnormal, melena, stomatitis, thirst; *Rare:* bloody diarrhea, cholecystitis, cholelithiasis, colitis, duodenal ulcer, enteritis, fecal incontinence, hematemesis, hepatitis, hepatomegaly, hyperchlorhydria, increased salivation, jaundice, liver tenderness, mouth ulceration, salivary gland enlargement, stomach ulcer, tongue discoloration, and tongue edema.

Endocrine System — *Infrequent:* hypothyroidism; *Rare:* goiter and hyperthyroidism.

Hemic and Lymphatic System — *Infrequent:* anemia and lymphadenopathy; *Rare:* bleeding time increased, blood dyscrasia, leukopenia, lymphocytosis, petechia, purpura, sedimentation rate increased, and thrombocythemia.

Metabolic and Nutritional — *Frequent:* weight loss; *Infrequent:* generalized edema, hypoglycemia, peripheral edema, and weight gain; *Rare:* dehydration, gout, hypercholesteremia, hyperglycemia, hyperlipemia, hypoglycemic reaction, hypokalemia, hyponatremia, and iron deficiency anemia.

Musculoskeletal System — *Infrequent:* arthritis, bone pain, bursitis, tenosynovitis, and twitching; *Rare:* bone necrosis, chondrodystrophy, muscle hemorrhage, myositis, osteoporosis, pathological fracture, and rheumatoid arthritis.

Nervous System — *Frequent:* abnormal dreams and agitation; *Infrequent:* abnormal gait, acute brain syndrome, akathisia, amnesia, apathy, ataxia, buccoglossal syndrome, CNS stimulation, convulsion, delusions, depersonalization, emotional lability, euphoria, hallucinations, hostility, hyperkinesia, hypesthesia, incoordination, libido increased, manic reaction, neuralgia, neuropathy, paranoid reaction, psychosis, and vertigo; *Rare:* abnormal electroencephalogram, antisocial reaction, chronic brain syndrome, circumoral paresthesia, CNS depression, coma, dysarthria, dystonia, extrapyramidal syndrome, hypertonia, hysteria, myoclonus, nystagmus, paralysis, reflexes decreased, stupor, and torticollis.

Respiratory System — *Frequent:* bronchitis, rhinitis, and yawn; *Infrequent:* asthma, epistaxis, hiccup, hyperventilation, and pneumonia; *Rare:* apnea, hemoptysis, hypoxia, larynx edema, lung edema, lung fibrosis/alveolitis, and pleural effusion.

Skin and Appendages — *Infrequent:* acne, alopecia, contact dermatitis, dry skin, herpes simplex, maculopapular rash, and urticaria; *Rare:* eczema, erythema multiforme, fungal dermatitis, herpes zoster, hirsutism, psoriasis, purpuric rash, pustular rash, seborrhea, skin discoloration, skin hypertrophy, subcutaneous nodule, and vesiculobullous rash.

Special Senses — *Infrequent:* amblyopia, conjunctivitis, ear pain, eye pain, mydriasis, photophobia, and tinnitus; *Rare:* blepharitis, cataract, corneal lesion, deafness, diplopia, eye hemorrhage, glaucoma, iritis, ptosis, strabismus, and taste loss.

Urogenital System — *Infrequent:* abnormal ejaculation, amenorrhea, breast pain, cystitis, dysuria, fibrocystic breast, impotence, leukorrhea, menopause, menorrhagia, ovarian disorder, urinary incontinence, urinary retention, urinary urgency, urination impaired, and vaginitis; *Rare:* abortion, albuminuria, breast enlargement, dyspareunia, epididymitis, female lactation, hematuria, hypomenorrhea, kidney calculus, metrorrhagia, orchitis, polyuria, pyelonephritis, pyuria, salpingitis, urethral pain, urethritis, urinary tract disorder, urolithiasis, uterine hemorrhage, uterine spasm, and vaginal hemorrhage.

Postintroduction Reports — Voluntary reports of adverse events temporally associated with Prozac that have been received since market introduction and which may have no causal relationship with the drug include the following: cerebral vascular accident, confusion, dyskinesia, ecchymoses, gastrointestinal hemorrhage, hyperprolactinemia, pancreatitis, suicidal ideation, thrombocytopenia, thrombocytopenic purpura, vaginal bleeding after drug withdrawal, and violent behaviors.

Overdosage: *Human Experience* — As of December 1987, there were two deaths among approximately 38 reports of acute overdose with fluoxetine, either alone or in combination with other drugs and/or alcohol. One death involved a combined overdose with approximately 1,800 mg of fluoxetine and an undetermined amount of maprotiline. A second death involved fluoxetine, codeine, and temazepam.

One other patient who reportedly took 3,000 mg of fluoxetine experienced two grand mal seizures that remitted spontaneously without specific anticonvulsant treatment. The actual amount of drug absorbed may have been less due to vomiting.

Nausea and vomiting were prominent in overdoses involving higher fluoxetine doses. Other prominent symptoms of overdose included agitation, restlessness, hypomania, and other signs of CNS excitation. Except for the two deaths noted above, all other overdose cases recovered without residua.

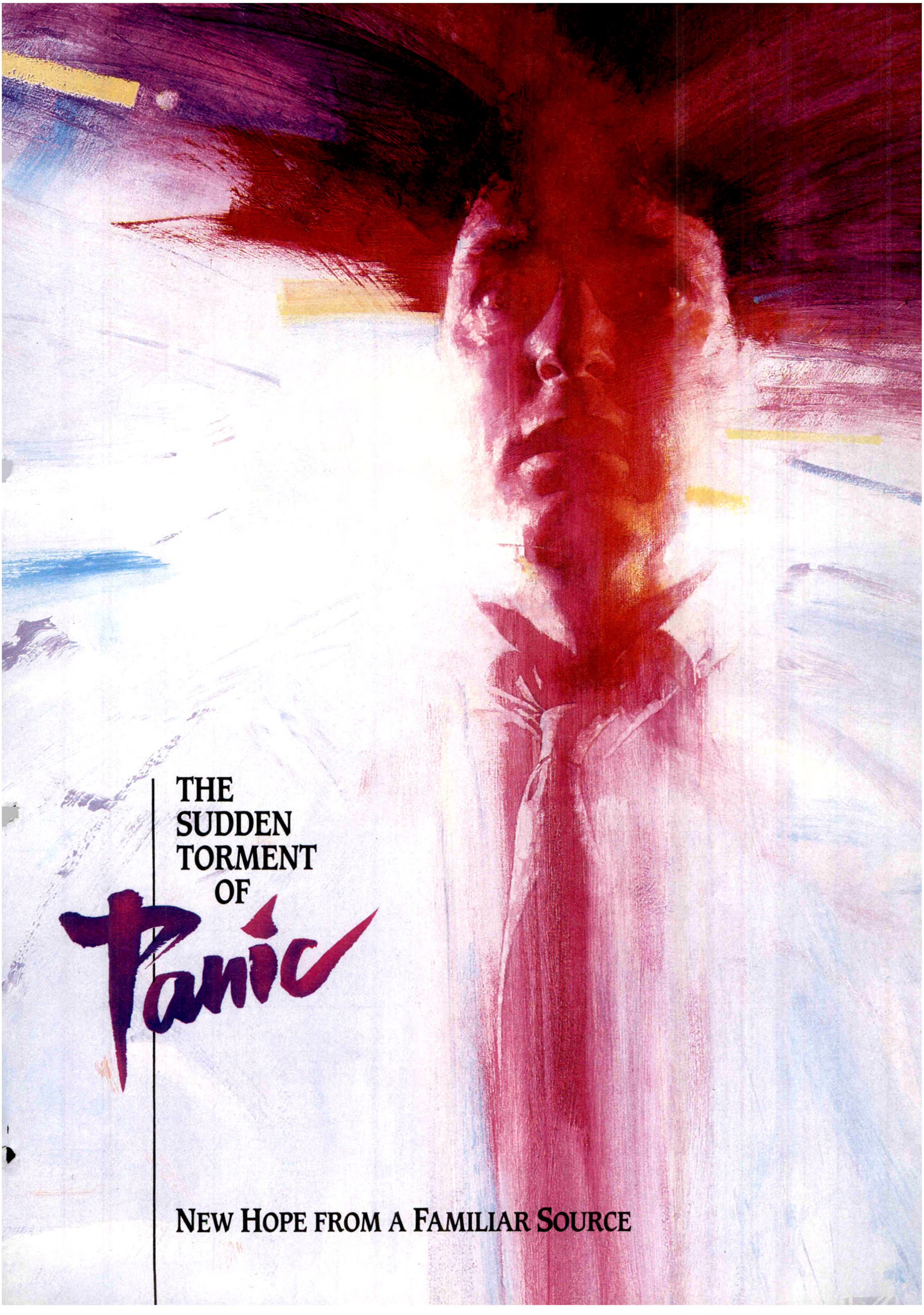
A single death attributed to overdose of fluoxetine alone has been reported.

PV 2478 DPP [052490]

Additional information available to the profession upon request.

Dista Products Company
Division of Eli Lilly and Company
Indianapolis, Indiana 46285

FL-4924-T-049337



THE SUDDEN TORMENT OF Panic

NEW HOPE FROM A FAMILIAR SOURCE

XANAX®: THE FIRST AND ONLY MEDICATION INDICATED FOR PANIC DISORDER

PANIC: A DISTINCT DIAGNOSTIC ENTITY

Panic disorder was classified as a distinct diagnostic entity for the first time by DSM-III in 1980.[1] The 1987 update (known as DSM-III-R)[2] further formalized the difference between panic disorder and generalized anxiety disorder.

THE DIAGNOSIS OF PANIC DISORDER

Panic attacks are discrete, time-limited episodes characterized by sudden, unexpected feelings of intense fear or discomfort. Accompanied by characteristic symptoms, these attacks involve specific cognitive and attitudinal changes.

A diagnosis of panic disorder, according to the DSM-III-R,[2] requires that a patient experience at least four panic attacks within a 4-week period or one or more attacks followed by a month of persistent fear of having another attack.

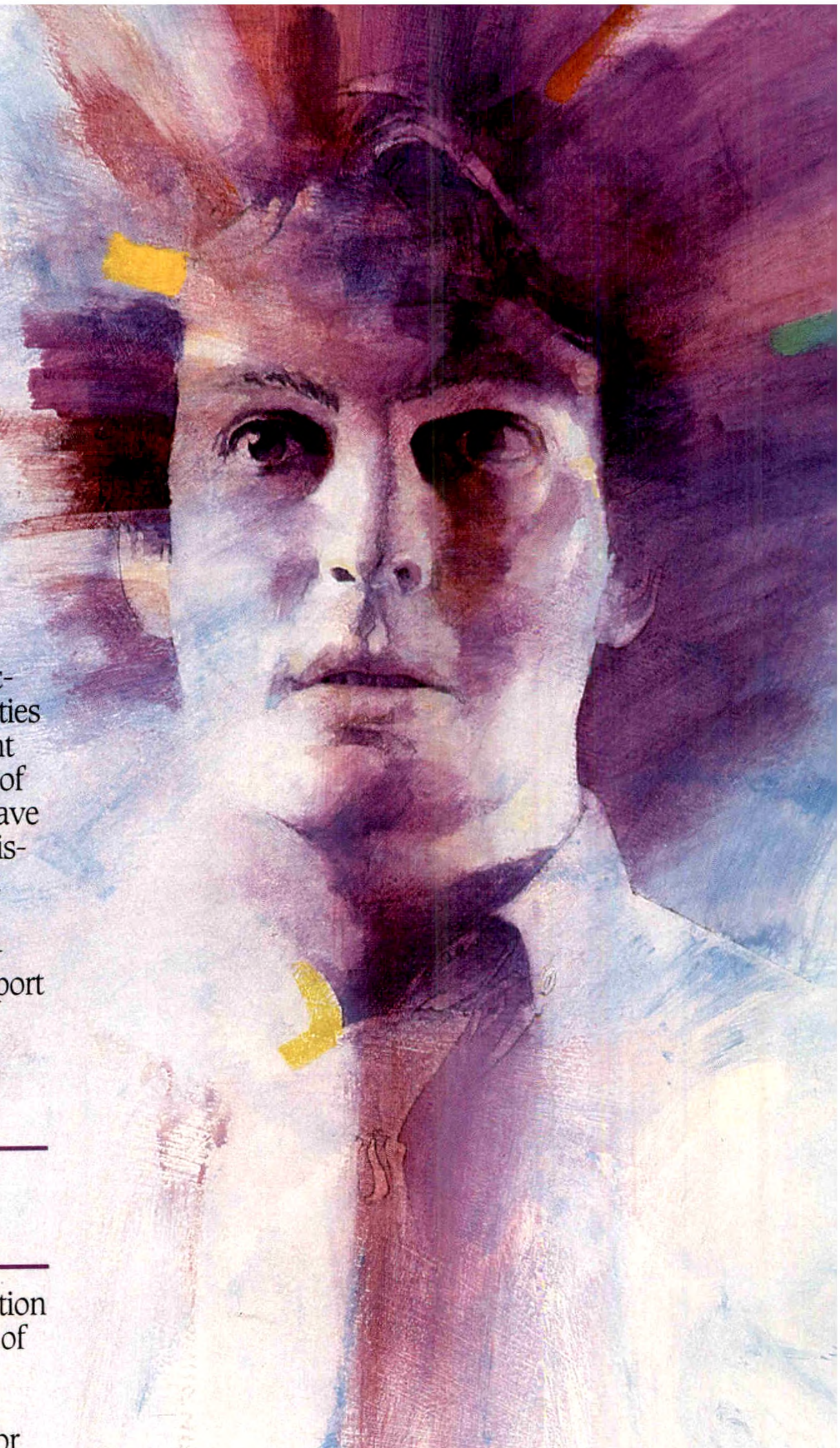
Panic attacks involve four or more of the characteristic associated symptoms, with no apparent organic cause. These symptoms develop suddenly and build in intensity within 10 minutes of the first symptom's onset.

Symptoms associated with panic attacks[2]

- Tachycardia or palpitations
- Chest pain or discomfort
- Sweating
- Shortness of breath (dyspnea) or smothering sensations
- Flushes (hot flashes) or chills
- Dizziness, unsteady feelings, or faintness
- Nausea or abdominal distress
- Choking
- Trembling or shaking
- Depersonalization or derealization
- Numbness or tingling sensations (paresthesias)
- Fear of dying
- Fear of going crazy or losing control

PANIC DISORDER AND PHOBIC AVOIDANCE

Most cases of panic disorder are accompanied by some degree of agoraphobia. This is the fear of being in places or situations from which escape might be difficult (or embarrassing) or in which help might be unavailable in the event of a panic attack.[2]



This fear often causes the panic-disorder patient to restrict daily activities dramatically, occasionally to the point of never leaving home. The majority of patients affected by panic disorder have a chronic, fluctuating course of the disorder for the better part of their adult lives.

Combining effective pharmacotherapy with psychotherapeutic support can significantly reduce or eliminate both panic attacks and associated phobic avoidance.

XANAX
FIRST FOR PANIC

XANAX is the first and only medication with an indication for the treatment of panic disorder with or without agoraphobia.

The effectiveness of XANAX for the treatment of panic disorder with or without agoraphobia was conclusively demonstrated in three placebo-controlled trials. The largest of these (the Cross-National Collaborative Panic Study) involved more than 500 patients in eight centers in the United States, Canada, and Australia.[3]

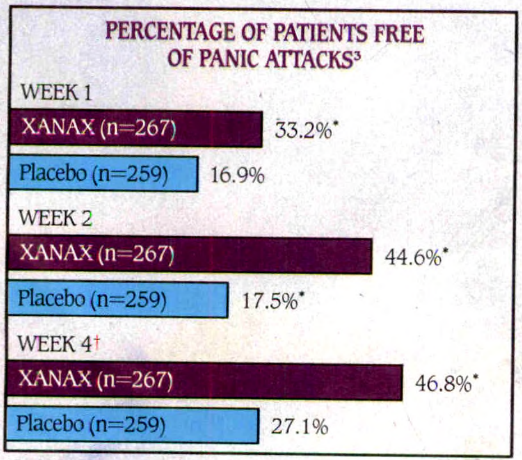
Tablets
Xanax®
alprazolam ⒸIV
FIRST FOR PANIC

Please see last page for references and brief summary of prescribing information.

PROVEN EFFICACY IN PANIC-DISORDER THERAPY

XANAX USUALLY BLOCKS PANIC ATTACKS WITHIN 1 WEEK

Patients in the Cross-National Collaborative Panic Study received XANAX or placebo on a relatively fixed-dosage schedule for 8 weeks. Evaluations were made at weeks 1, 2, 3, 4, 6, and 8 of therapy.



*$P < .001$

†End-point analysis involving all patients

XANAX produced significant relief from panic attacks compared with placebo by the end of the first week of therapy. Nearly half of the patients who received XANAX were free from panic attacks by the end of short-term therapy.[3]

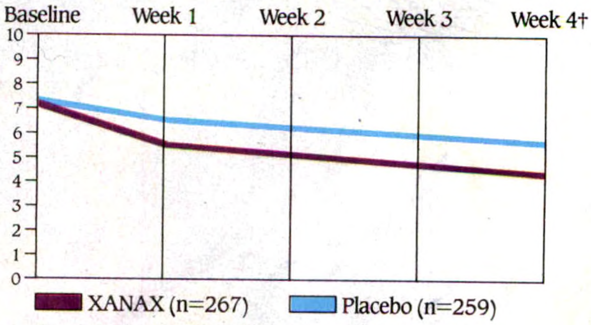
Because of the high rate of placebo dropouts, week 4 (the last evaluation point where the majority of patients remained in the placebo treatment group) was considered the study "end point" for efficacy analyses.

XANAX REDUCES PHOBIC AVOIDANCE

The majority of patients enrolled in the Cross-National Collaborative Panic Study (84%) were diagnosed with agoraphobia with panic attacks.[3]

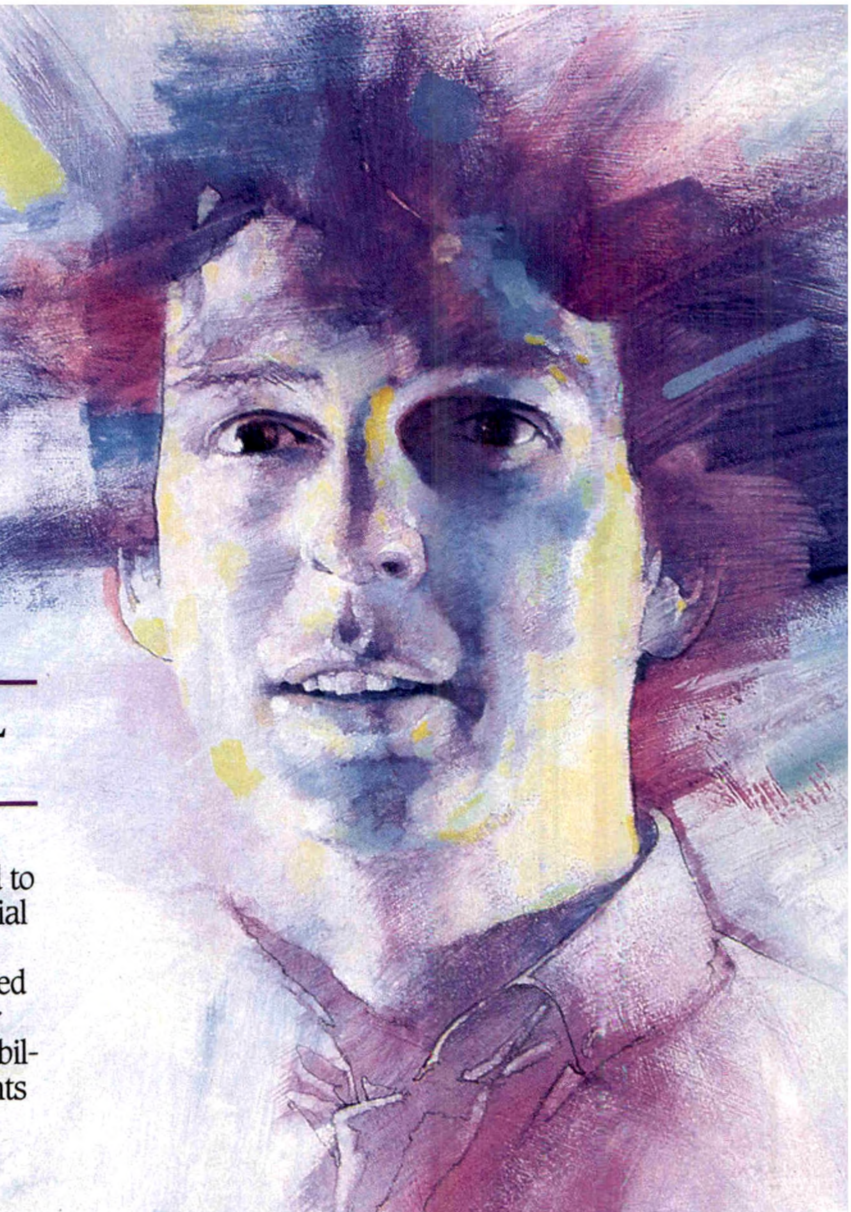
Phobic symptoms were measured on a 0 to 10 phobia rating scale, where 0 = no phobias and 10 = extreme distress. Patients who received XANAX experienced significantly greater reductions in overall phobic symptoms at each evaluation week compared with placebo-treated patients.[3]

MEAN OVERALL PHOBIC-SYMPTOM RATING[3]*



*Zero to 10 scale, where 0 = no phobias and 10 = extremely distressing

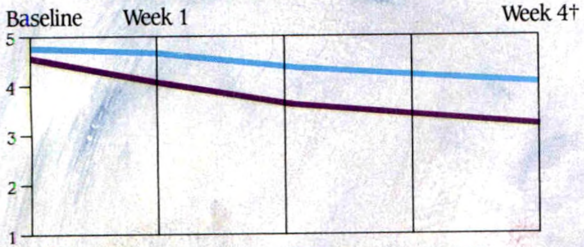
†End-point analysis involving all patients



XANAX REDUCES SOCIAL AND WORK DISABILITY

When patients in the Cross-National Collaborative Panic Study were asked to indicate the extent to which their social life and work abilities were impaired by their disorder, patients who received XANAX showed significantly greater improvement in work and social disability scale scores compared with patients who received placebo.[3]

MEAN WORK IMPAIRMENT RATING[3]*



*Zero to 10 scale, where 0 = not at all, 5 = moderately impaired, and 10 = severely impaired

†End-point analysis involving all patients

Tablets
Xanax®
alprazolam Ⓒ IV
FIRST FOR PANIC

Please see last page for references and brief summary of prescribing information.

PROPER DOSING OF XANAX: ESSENTIAL TO SUCCESS

The usual starting dose for panic patients is 0.5 mg t.i.d. Depending on the patient's response, the total daily dose can then be adjusted upward in increments no greater than 1 mg every 3 to 4 days to a maximum of 10 mg/day. Some patients may require a slower dosage titration. In clinical studies, the average daily dose after 8 weeks was 5.7 mg. The risk of dependence and its severity appear to be greater in patients treated with relatively high doses (above 4 mg/day) and for long periods (more than 8 to 12 weeks), as required by panic patients.

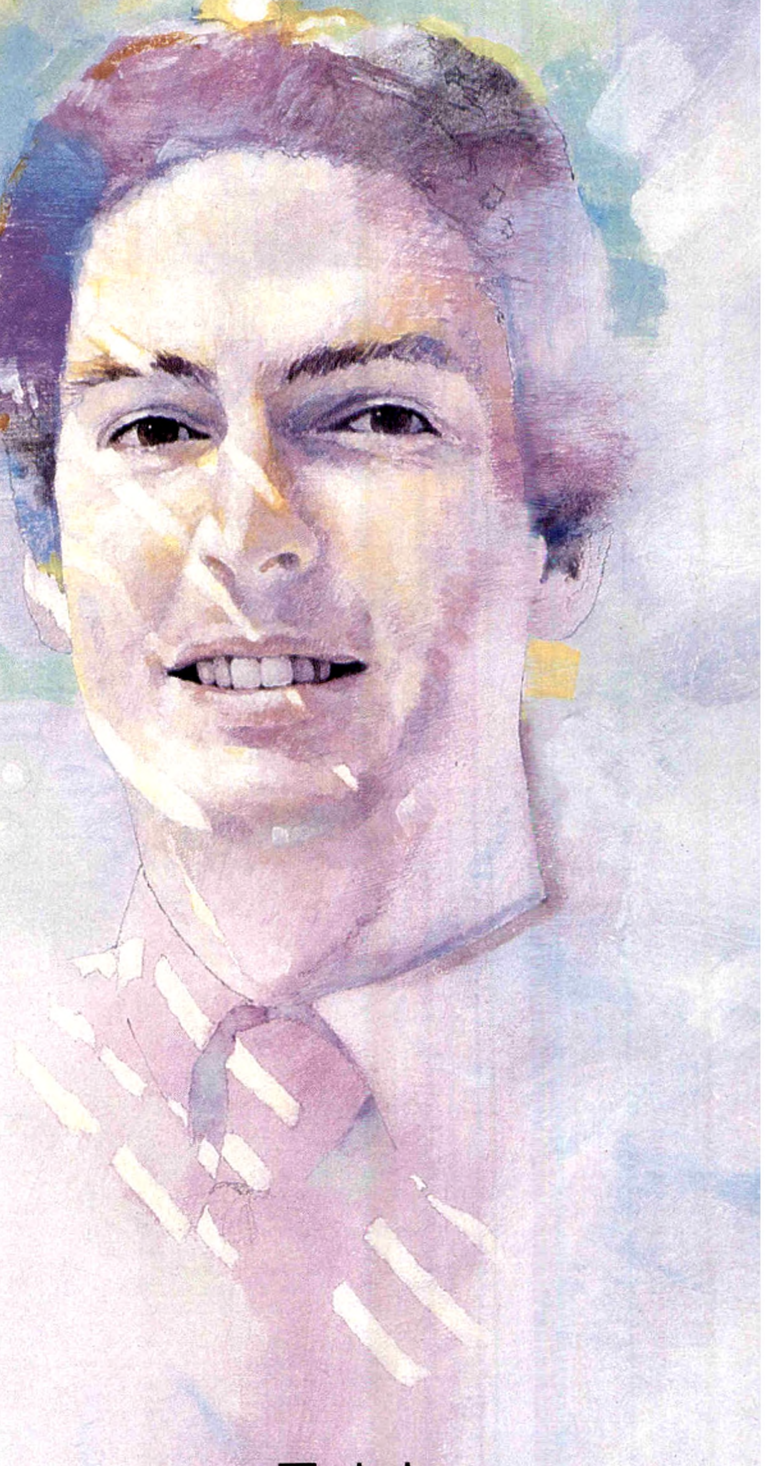
Continue incremental dosage adjustment until adequate control of panic attacks is achieved and phobic symptoms are reduced.

SIDE EFFECTS

Most treatment-emergent symptoms and side effects reported by patients who received XANAX were those generally associated with benzodiazepine therapy, such as drowsiness/sedation and ataxia/impaired coordination. At least mild sedation was reported by 77% of patients who received therapy with XANAX Tablets and by 43% of patients on placebo. Side effects are generally observed at the beginning of therapy and usually disappear upon continued medication or decreased dosage.

MAINTENANCE AND TAPERING

The necessary duration of treatment for panic-disorder patients responding to XANAX is unknown. After a period of extended freedom from attacks, a carefully supervised, tapered discontinuation may be attempted. Dosage reduction must be individualized according to patient response, and the length of time will depend in part on the dosage level attained. There is evidence that discontinuation may be exceedingly difficult for some patients to accomplish without recurrence of panic-disorder symptoms or the development of withdrawal phenomena.



Dosage should be reduced gradually, never abruptly, by not more than 1 mg per week until a total daily dose of 4 mg is achieved; by 0.5 mg/week until a total daily dose of 2 mg is reached; and by 0.25 mg/week thereafter. Some patients may require an even slower tapering of dosage. Withdrawal reactions may occur when dosage reduction occurs for any reason. This not only includes purposeful tapering but also inadvertent reduction of dose. Therefore, the dosage of XANAX should be reduced or discontinued gradually.

NEW 2-MG XANAX TABLETS FOR PANIC

- Greater convenience in maintenance dosages
- Scored to allow incremental dosing (0.5 mg, 1 mg, or 2 mg)
- New tablet strength more economical for patients

Tablets
Xanax®
alprazolam CIV
FIRST FOR PANIC

Please see last page for references and brief summary of prescribing information.

XANAX® Tablets
(alprazolam, © Upjohn)

INDICATIONS AND USAGE

Generalized anxiety disorder, short-term relief of the symptoms of anxiety, and anxiety associated with depression. Anxiety or tension associated with the stress of everyday life usually does not require an anxiolytic.

Panic disorder, with or without agoraphobia.

Effectiveness has been established for up to 4 months for anxiety disorder and 4 to 10 weeks for panic disorder; but panic disorder has been treated open label for up to 8 months with no apparent loss of benefit. The usefulness should be reassessed periodically.

CONTRAINDICATIONS

Sensitivity to XANAX or other benzodiazepines and in acute narrow-angle glaucoma.

WARNINGS

Dependence and withdrawal reactions, including seizures

Physical dependence to XANAX can produce certain adverse clinical events, some life-threatening. These include a spectrum of withdrawal symptoms—the most important is seizure. Even after relatively short-term use at 0.75 to 4 mg per day, there is some risk of dependence; but the risk and severity seem to be greater in patients treated with doses above 4 mg/day for more than 8 to 12 weeks.

Treatment of panic disorder: Dose and risks of XANAX

Panic-disorder patients often need doses greater than 4 mg/day, hence the risk of dependence may be greater than in patients treated for less severe anxiety. Based on studies involving 641 patients, the most frequent symptoms seen during discontinuation were:

Neurologic: Insomnia, light-headedness, abnormal involuntary movement, headache, muscular twitching, impaired coordination, muscle-tone disorders, weakness.

Psychiatric: Anxiety, fatigue and tiredness, irritability, cognitive disorder, memory impairment, depression, confusional state.

Gastrointestinal: Nausea/vomiting, diarrhea, decreased salivation.

Other systems: Weight loss, decreased appetite, sweating, tachycardia, blurred vision. It has not yet been determined if these symptoms are clearly related to dose and duration of therapy. In two controlled trials of the discontinuation of XANAX lasting 6 to 8 weeks, 71% to 93% of patients treated with XANAX compared with 89% to 96% of placebo patients tapered completely off medication. The ability of patients to completely discontinue after long-term therapy has not been reliably determined.

Seizures were reported in 8 of 1,980 patients who took more than 4 mg XANAX daily for over 3 months, generally during abrupt dose reduction. There have been occasional reports of seizures during gradual taper; the risk seems to be greatest 24 to 72 hours after discontinuation.

Status epilepticus and its treatment: Discontinuation of XANAX has been associated with seizures. In most cases a single seizure was reported; however, multiple seizures and status epilepticus have been reported. Treatment is the same as that for status of any cause.

Interdose symptoms: Early morning anxiety and emergence of anxiety symptoms between doses have been reported in panic patients taking XANAX. It can usually be managed with more frequent administration of the same total daily dose or by increasing total dosage.

Risks of dose reduction: Withdrawal reactions may occur with dosage reduction for any reason; dosage should be reduced gradually. (See DOSAGE AND ADMINISTRATION.)

XANAX is not of value in treating psychosis and should not be used in lieu of appropriate treatment. Patients receiving XANAX should be cautioned about hazardous occupations or activities requiring full alertness and also about simultaneous ingestion of alcohol or other CNS depressants.

Benzodiazepines can cause fetal harm in pregnant women, hence women who may become pregnant should be warned. Avoid during the first trimester. (See DRUG ABUSE AND DEPENDENCE and DOSAGE AND ADMINISTRATION.)

PRECAUTIONS

General: If XANAX is combined with other psychotropics or anticonvulsants, consider drug potentiation. (See DRUG INTERACTIONS.) Use the usual precautions in patients with impaired renal, hepatic, or pulmonary function and regarding prescription size in depressed and suicidal patients. Use the smallest effective dose to avoid ataxia or oversedation, which may be a particular problem in elderly or debilitated patients. Alprazolam plasma half-life may be prolonged in obese patients or those with alcoholic liver disease. There have been rare reports of death in patients with severe pulmonary disease shortly after the start of therapy with XANAX. Episodes of mania and hypomania have been reported in depressed patients. Alprazolam is weakly uricosuric.

Information for patients: For all users of XANAX. Alert patients about: (1) consumption of alcohol and drugs, (2) not taking any benzodiazepine during pregnancy or while nursing, (3) operating machinery or driving, (4) not increasing the dose due to risk of dependence, (5) not stopping the drug abruptly.

Additional advice for panic patients:

Use of more than 4 mg per day of XANAX for long periods of time may cause severe emotional and physical dependence in some patients, and these patients may find it difficult to stop treatment. In two studies lasting 6 to 8 weeks, 7% to 29% of patients treated with XANAX did not completely taper off therapy. The ability of patients to completely discontinue therapy has not been determined. Also, extended use of high doses appears to increase the incidence and severity of withdrawal reactions when XANAX is discontinued. These are generally minor, but seizure, which can be life-threatening, can occur, especially if dose is reduced too rapidly or stopped abruptly.

Laboratory tests: Not ordinarily required in otherwise healthy patients.

Drug interactions: Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol, and other CNS depressants. Plasma levels of imipramine and desipramine are increased. Pharmacokinetic interactions with other drugs have been reported. Cimetidine and oral contraceptives can delay clearance of benzodiazepines. ***Drug/laboratory test interactions:*** No consistent pattern. ***Carcinogenesis, mutagenesis, impairment of fertility:*** No carcinogenic potential or impairment of fertility in rats. ***Pregnancy:*** See WARNINGS. ***Nonteratogenic effects:*** The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms, neonatal flaccidity, and respiratory problems. ***Labor and delivery:*** No established use. ***Nursing mothers:*** Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. ***Pediatric use:*** Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS

Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacologic activity of XANAX, eg, drowsiness or light-headedness.

Central nervous system: Drowsiness, light-headedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness. Impaired coordination, irritability, memory impairment, cognitive disorder, dysarthria, anxiety, abnormal involuntary movement, changed libido, muscular twitching, weakness, muscle-tone disorders, agitation, disinhibition, paresthesia, talkativeness, vasomotor disturbances, derealization, dream abnormalities, fear, feeling warm.

Gastrointestinal: Dry mouth, constipation, diarrhea, nausea/vomiting, increased salivation, decreased salivation, and abdominal distress.

Cardiorespiratory: Tachycardia/palpitations, hypotension, nasal congestion, chest pain, hyperventilation, upper respiratory infection.

Other: Blurred vision, rigidity and tremor, tinnitus, muscular stiffness and cramps, sweating, skin disorders, rash, change in appetite, micturition difficulties, menstrual disorders, sexual dysfunction, edema, incontinence, infection, dermatitis/allergy, weight gain, and weight loss.

Withdrawal seizures with rapid decrease or abrupt discontinuation. (See WARNINGS.)

To discontinue treatment, dosage must be reduced slowly by no more than 0.5 mg every 3 days.

The following adverse events have been reported with benzodiazepines: dystonia, concentration difficulties, anorexia, slurred speech, jaundice, pruritus, diplopia.

Untreated panic disorder has been associated with depressive disorders and suicide. When treating panic patients, the same caution must be used as in treating patients with depression or suicidal ideation.

Paradoxical reactions such as stimulation, agitation, rage, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes, of unknown significance, have been observed.

Liver enzyme elevations, gynecomastia, and galactorrhea have been reported but no causal relationship was established.

DRUG ABUSE AND DEPENDENCE

Physical and psychologic dependence: Withdrawal symptoms like those noted with sedative/hypnotics and alcohol have been seen after discontinuance of benzodiazepines. Symptoms can range from mild dysphoria and insomnia to a major syndrome including abdominal and muscle cramps, vomiting, sweating, tremors, and convulsions. The distinction between withdrawal symptoms and recurrence of illness is difficult. Withdrawal typically includes new symptoms, occurs toward the end of taper or shortly after discontinuation, and decreases with time. Recurrent panic disorder recurs early or late, with persistent symptoms similar to the initial presentation. When necessary XANAX should be restarted in adequate dosage.

Withdrawal symptoms, including seizures, may occur after brief therapy with doses of 0.75 to 4 mg/day, but severity and incidence are apparently increased after doses above 4 mg/day, after rapid decrease of dosage or abrupt discontinuation. Dosage should be gradually tapered under close supervision, especially in patients with a history of seizures or epilepsy.

Psychologic dependence is a risk with all benzodiazepines, increasing at higher doses, with long-term use, and in patients with a history of alcohol or drug abuse. Addiction-prone patients should be closely supervised when receiving XANAX and repeat prescriptions limited.

Controlled Substance Class: XANAX is a controlled substance and has been assigned to schedule IV.

OVERDOSAGE

Manifestations include somnolence, confusion, impaired coordination, diminished reflexes, and coma. Death has been reported with overdosage of benzodiazepines by themselves or in combination with overdosage of alcohol.

DOSAGE AND ADMINISTRATION

Dosage should be individualized, using the lowest effective dose. The need for treatment should be reassessed frequently.

Anxiety: The usual starting dose is .25 to 0.5 mg t.i.d. Maximum daily dose is 4 mg. Patients who are elderly or debilitated, or have advanced liver disease, may be especially sensitive to benzodiazepines, and the starting dose is 0.25 mg b.i.d. or t.i.d. Reduce dosage gradually, by no more than 0.5 mg every 3 days, or more slowly.

Panic disorder: Many patients required more than 4 mg daily. Mean dosage in studies was 5 to 6 mg/day, with a maximum of 10 mg/day. Treatment may be initiated with 0.5 mg t.i.d. Depending on the response, dose may be increased every 3 or 4 days by up to 1 mg daily. After extended freedom from attacks, dosage should be carefully tapered by, at most, 0.5 mg every 3 days. Some patients may be resistant to all discontinuation regimens.

HOW SUPPLIED

XANAX Tablets are available in 0.25-mg, 0.5-mg, 1-mg, and 2-mg strengths.

CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION.

References:

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Third Edition.* Washington, DC: American Psychiatric Association; 1980:230-232.
2. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised.* Washington, DC: American Psychiatric Association; 1987:236-238.
3. Ballenger JC, Burrows GD, DuPont RL Jr, et al. Alprazolam in panic disorder and agoraphobia: results from a multicenter trial, I: efficacy in short-term treatment. *Arch Gen Psychiatry.* 1988;45:413-422.

Upjohn THE UPJOHN COMPANY
Kalamazoo, Michigan 49001, USA
Printed in USA

B-9-S
J 8709
October 1990

HALDOL® Decanoate 100

(HALOPERIDOL) INJECTION 100mg/mL

HALDOL® Decanoate 50

(HALOPERIDOL) INJECTION 50mg/mL

For IM Injection Only

The following is a brief summary only. Before prescribing, see complete prescribing information in HALDOL and HALDOL Decanoate product labeling.

Contraindications: Since the pharmacologic and clinical actions of HALDOL Decanoate 50 and HALDOL Decanoate 100 are attributed to HALDOL haloperidol as the active medication. Contraindications, Warnings, and additional information are those of HALDOL, modified to reflect the prolonged action.

HALDOL is contraindicated in severe toxic central nervous system depression or comatose states from any cause and in individuals who are hypersensitive to this drug or have Parkinson's disease.

Warnings: *Tardive Dyskinesia:* Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown. Both the risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown. Given these considerations, antipsychotic drugs should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that 1) is known to respond to antipsychotic drugs, and 2) for whom alternative, equally effective, but potentially less harmful treatments are **not** available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically. If signs and symptoms of tardive dyskinesia appear in a patient on antipsychotics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome. (For further information about the description of tardive dyskinesia and its clinical detection, please refer to ADVERSE REACTIONS.)

Neuroleptic Malignant Syndrome (NMS): A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status (including catatonic signs) and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure. The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology. The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS. If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported. Hyperpyrexia and heat stroke, not associated with the above symptom complex, have also been reported with HALDOL.

Usage in Pregnancy: (see PRECAUTIONS—Usage in Pregnancy) *Combined Use With Lithium:* (see PRECAUTIONS—Drug Interactions)

General: Bronchopneumonia, sometimes fatal, has followed use of antipsychotic drugs, including haloperidol. Prompt remedial therapy should be instituted if dehydration, hemoconcentration or reduced pulmonary ventilation occur, especially in the elderly. Decreased serum cholesterol and/or cutaneous and ocular changes have been reported with chemically-related drugs, although not with haloperidol. See PRECAUTIONS—Information for Patients for information on mental and/or physical abilities and on concomitant use with other substances.

Precautions: Administer cautiously to patients: (1) with severe cardiovascular disorders, due to the possibility of transient hypotension and/or precipitation of anginal pain (if a vasopressor is required, epinephrine should not be used since HALDOL may block its vasopressor activity and paradoxical further lowering of blood pressure may occur; metaraminol, phenylephrine or norepinephrine should be used); (2) receiving anticonvulsant medications, with a history of seizures, or with EEG abnormalities, because HALDOL may lower the convulsive threshold. If indicated, adequate anticonvulsant therapy should be concomitantly maintained; (3) with known allergies or a history of allergic reactions to drugs; (4) receiving anticoagulants, since an isolated instance of interference occurred with the effects of one anticoagulant (phenindione). Concomitant antiparkinson medication, if required, may have to be continued after HALDOL is discontinued because of different excretion rates; if both are discontinued simultaneously, extrapyramidal symptoms may occur. Intraocular pressure may increase when anticholinergic drugs, including antiparkinson drugs, are administered concomitantly with HALDOL. When HALDOL is used for mania in bipolar disorders, there may be a rapid mood swing to depression. Severe neurotoxicity may occur in patients with thyrotoxicosis receiving antipsychotic medication, including HALDOL.

The 1, 5, 10 mg HALDOL tablets contain FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals, especially in those who have aspirin hypersensitivity.

Information for Patients: Mental and/or physical abilities required for hazardous tasks or driving may be impaired. Alcohol should be avoided due to possible additive effects and hypotension.

Drug Interactions: Patients receiving lithium plus haloperidol should be monitored closely for early evidence of neurological toxicity and treatment discontinued promptly if such signs appear. As with other antipsychotic agents, it should be noted that HALDOL may be capable of potentiating CNS depressants such as anesthetics, opiates, and alcohol.

Carcinogenesis, Mutagenesis and Impairment of Fertility: No mutagenic potential of haloperidol decanoate was found in the Ames Salmonella microsomal activation assay.

Carcinogenicity studies using oral haloperidol were conducted in Wistar rats (dosed at up to 5 mg/kg daily for 24 months) and in Albino Swiss mice (dosed at up to 5 mg/kg daily for 18 months). In the rat study survival was less than optimal in all dose groups, reducing the number of rats at risk for developing tumors. However, although a relatively greater number of rats survived to the end of the study in high dose male and female groups, these animals did not have a greater incidence of tumors than control animals. Therefore, although not optimal, this study does suggest the absence of a haloperidol related increase in the incidence of neoplasia in rats at doses up to 20 times the usual daily human dose for chronic or resistant patients. In female mice at 5 and 20 times the highest initial daily dose for chronic or resistant patients, there was a statistically significant increase in mammary gland neoplasia and total tumor incidence; at 20 times the same daily dose there was a statistically significant increase in pituitary gland neoplasia. In male mice, no statistically significant differences in incidences of total tumors or specific tumor types were noted.

Antipsychotic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of antipsychotic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

Usage in Pregnancy: Pregnancy Category C. Safe use in pregnancy or in women likely to become pregnant has not been established; use only if benefit clearly justifies potential hazards to the fetus.

Nursing Mothers: Infants should not be nursed during drug treatment.

Pediatric Use: Controlled trials to establish the safety and effectiveness of intramuscular administration in children have not been conducted.

Adverse Reactions: Adverse reactions following the administration of HALDOL Decanoate 50 or HALDOL Decanoate 100 are those of HALDOL haloperidol. Since vast experience has accumulated with HALDOL, the adverse reactions are reported for that compound as well as for haloperidol decanoate. As with all injectable medications, local tissue reactions have been reported with haloperidol decanoate.

CNS Effects: Extrapyramidal Reactions—Neuromuscular (extrapyramidal) reactions have been reported frequently, often during the first few days of treatment. Generally they involved Parkinson-like symptoms which when first observed were usually mild to moderately severe and usually reversible. Other types of neuromuscular reactions (motor restlessness, dystonia, akathisia, hyperreflexia, opisthotonos, oculogyric crises) have been reported far less frequently, but were often more severe. Severe extrapyramidal reactions have been reported at relatively low doses. Generally, extrapyramidal symptoms are dose-related since they occur at relatively high doses and disappear or become less severe when the dose is reduced. Antiparkinson drugs may be required. Persistent extrapyramidal reactions have been reported and the drug may have to be discontinued in such cases. *Withdrawal Emergent Neurological Signs*—Abrupt discontinuation of short-term antipsychotic therapy is generally uneventful. However, some patients on maintenance treatment experience transient dyskinetic signs after abrupt withdrawal. In certain cases these are indistinguishable from "Tardive Dyskinesia" except for duration. It is unknown whether gradual withdrawal will reduce the occurrence of these signs, but until further evidence is available HALDOL should be gradually withdrawn. *Tardive Dyskinesia*—As with all antipsychotic agents HALDOL has been associated with persistent dyskinesias. Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may appear in some patients on long-term therapy or may occur after drug therapy has been discontinued. The risk appears to be greater in elderly patients on high-dose therapy, especially females. The symptoms are persistent and in some patients irreversible. The syndrome is characterized by rhythmical involuntary movements of tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities and the trunk. There is no known effective treatment for tardive dyskinesia; antiparkinson agents usually do not alleviate the symptoms of this syndrome. It is suggested that all antipsychotic agents be discontinued if these symptoms appear. Should it be necessary to reinstitute treatment, or increase the dosage of the agent, or switch to a different antipsychotic agent, this syndrome may be masked. It has been reported that fine vermicular movement of the tongue may be an early sign of tardive dyskinesia and if the medication is stopped at that time the full syndrome may not develop. *Tardive Dystonia*—Tardive dystonia, not associated with the above syndrome, has also been reported. Tardive dystonia is characterized by delayed onset of choreic or dystonic movements, is often persistent, and has the potential of becoming irreversible. *Other CNS Effects*—Insomnia, restlessness, anxiety, euphoria, agitation, drowsiness, depression, lethargy, headache, confusion, vertigo, grand mal seizures, and exacerbation of psychotic symptoms including hallucinations, and catatonic-like behavioral states which may be responsive to drug withdrawal and/or treatment with anticholinergic drugs.

Body as a Whole: Neuroleptic malignant syndrome (NMS), hyperpyrexia and heat stroke have been reported with HALDOL. (See WARNINGS for further information concerning NMS.) *Cardiovascular Effects:* Tachycardia, hypotension, hypertension and ECG changes. *Hematologic Effects:* Reports of mild, usually transient leukopenia and leukocytosis, minimal decreases in red blood cell counts, anemia, or a tendency toward lymphomonocytosis; agranulocytosis rarely reported and only in association with other medication. *Liver Effects:* Impaired liver function and/or jaundice. *Dermatologic Reactions:* Maculopapular and acneiform reactions, isolated cases of photosensitivity, loss of hair. *Endocrine Disorders:* Lactation, breast engorgement, mastalgia, menstrual irregularities, gynecomastia, impotence, increased libido, hyperglycemia, hypoglycemia and hyponatremia. *Gastrointestinal Effects:* Anorexia, constipation, diarrhea, hypersalivation, dyspepsia, nausea and vomiting. *Autonomic Reactions:* Dry mouth, blurred vision, urinary retention, diaphoresis, and priapism. *Respiratory Effects:* Laryngospasm, bronchospasm and increased depth of respiration. *Special Senses:* Cataracts, retinopathy and visual disturbances. *Other:* Cases of sudden and unexpected death have been reported in association with the administration of HALDOL. The nature of the evidence makes it impossible to determine definitively what role, if any, HALDOL played in the outcome of the reported cases. The possibility that HALDOL caused death cannot, of course, be excluded, but it is to be kept in mind that sudden and unexpected death may occur in psychotic patients when they go untreated or when they are treated with other antipsychotic drugs.

IMPORTANT: Full directions for use should be read before HALDOL or HALDOL Decanoate products are administered or prescribed.

For information on symptoms and treatment of overdosage, see full prescribing information.

The short-acting HALDOL injectable form is intended only for acutely agitated psychotic patients with moderately severe to very severe symptoms.

McNeil Pharmaceutical, McNEILAB, INC., Spring House, PA 19477

8/23/89

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HALDOL® Decanoate 100
(HALOPERIDOL) INJECTION

Less volume per injection can enhance patient acceptance

100 mg/mL formulation is twice the concentration of the original 50 mg/mL decanoate formulation

- For many patients, fewer injections per dose may reduce anxiety and enhance patient compliance
- Multi-dose vial packaging means convenience for you and your staff

Please see brief summary of Prescribing Informatio on the preceding page.

During dose adjustment or episodes of exacerbation of psychotic symptoms, therapy with HALDOL Decanoate 100 or HALDOL Decanoate 50 can be supplemented with short-acting forms of HALDOL® (haloperidol). The side effects of the decanoate products are those of HALDOL. The prolonged action of HALDOL Decanoate 100 and HALDOL Decanoate 50 should be considered in the management of side effects.

HALDOL® Decanoate 100
(HALOPERIDOL) INJECTION 100mg/mL
HALDOL® Decanoate 50
(HALOPERIDOL) INJECTION 50mg/mL

McNEIL PHARMACEUTICAL
SPRING HOUSE, PA 19477-0776

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